VETERANS HEALTH ADMINISTRATION

CLINICAL GUIDELINES
FOR
MANAGEMENT OF PATIENTS WITH DIABETES MELLITUS

VETERANS HEALTH ADMINISTRATION
CLINICAL GUIDELINE FOR
MANAGEMENT OF DIABETES MELLITUS

Prepared by

The Diabetes Mellitus Working Group*

With support from
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and

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***See Directory in Appendices for Listing of Participants**

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VETERANS HEALTH ADMINISTRATION
CLINICAL GUIDELINE FOR THE
MANAGEMENT OF DIABETES MELLITUS

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INTRODUCTION

INTRODUCTION

These clinical practice guidelines on the assessment and treatment of diabetes mellitus are intended to facilitate the management of persons with diabetes seen in specialty as well as primary care settings. The guidelines are broad enough to encompass the critical decision points in patient management, such as glycemic control, evaluation of the eyes and feet, and early recognition and treatment of co-morbid conditions including hypertension, hyperlipidemia, and renal disease. At the same time, they are designed to be flexible so that local policies or procedures, such as those regarding referrals to or consultation with diabetes teams, ophthalmology, optometry, podiatry, nephrology, and endocrinology (lipids), can be accommodated. Medication usage guidelines have been adapted from the Pharmacy Benefits Management Strategic Health Group Medical Advisory Panel Guidelines for Non-Insulin Dependent Diabetes Mellitus (NIDDM), Hypertension and Cholesterol.

DEFINITIONS

The Veterans Health Administration defines Clinical Practice Guidelines as[1]:

> Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes the following:
>
> - Determination of appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction, and
>
> - Literature review to determine the strength of the evidence (based in part on study design) in relation to these criteria.

Clinical practice guidelines are frequently displayed in the form of an algorithm (an algorithm is a set of rules for solving a problem in a finite number of steps). Typically, a clinical algorithm diagrams a guideline into a step-by-step decision tree. VHA's clinical practice guideline for diabetes mellitus is displayed in algorithmic format.

Clinical practice guidelines, which are being used increasingly in health care, are seen by many as a potential solution to inefficiency and inappropriate variation in care. Guidelines should be evidence-based and based upon explicit criteria, to ensure consensus regarding their internal validity.[2, 3] However, it is acknowledged that the use of guidelines must always be in the context of a provider's clinical judgment in the care of a particular person. For that reason, the guidelines may be viewed as an educational tool analogous to textbooks and journals, but in an user-friendlier format.

Clinical Pathways are defined as:

- Clinical management tools that organize, sequence, and specify the timing for the major patient care activities and interventions of the entire interdisciplinary team for a particular diagnosis or procedure. Clinical Pathways define key processes and events in the day-to-day management of care and often serve as a component of the patient record. Variance from the pathway along with causes of variance should be documented.

OVERVIEW OF THE DIABETES GUIDELINES:

The diabetes mellitus guidelines are organized into six major modules, with a linkage diabetes algorithm providing an overview of the relationship between the modules:

- **Module G**—Glycemic Control:
  - **GM**—Medication
  - **GN**—Nutrition
  - **GH**—Home Monitor
  - **GP**—Physical Activity

- **Module F**—Foot Care:
  - **FR**—Routine Foot Care
  - **FI**—Infection and Ulcers

- **Module E**—Eye Care
- **Module H**—Hypertension Management
- **Module L**—Lipid Control
- **Module R**—Renal Disease Treatment

Diabetes prevention strategies can be conceptually divided into three categories: Primary Prevention, Secondary Prevention, and Tertiary Prevention. ***Primary prevention*** refers to the prevention of the onset of diabetes. Although National Institutes of Health sponsored controlled, randomized, clinical trials of primary prevention of Type I and Type II diabetes in high-risk individuals are underway, it will be years before the results are available. ***Secondary prevention*** in diabetes is the concept that improved glycemic control will result in a decrease in the development of microvascular complications. Finally, ***tertiary prevention*** is the premise that screening for the presence of early microvascular disease (such as retinopathy, nephropathy, and neuropathy) will lead to the identification of individuals for whom therapeutic interventions can reduce their subsequent risk of blindness, renal failure and amputation. Each module uses a **risk stratification approach** to identify persons with diabetes who have a greater probability of developing complications, and who therefore would benefit from more intensive intervention.

Finally, providers should recognize that the major cause of morbidity and mortality in persons with diabetes is cardiovascular disease — myocardial infarction, stroke, and peripheral vascular disease. It accounts for over 70% of hospitalizations and deaths. Therefore an aggressive approach to evaluating and reducing cardiovascular risk factors — including smoking cessation, management of hyperlipidemia, treatment of hypertension, and promotion of a healthy lifestyle — should be a general goal for all providers.

While each module is designed for use by primary care providers in an ambulatory care setting, the modules can also be used to coordinate and standardize care within subspecialty teams, and as teaching tools for students and housestaff. However, it should be recognized that this series of algorithms, as is true for most, cannot be used as a linear guideline for the recognition and management of diabetes mellitus and are not intended to supersede the clinical judgment of the provider caring for an individual.

The majority of the literature support for these guidelines, referenced throughout the document, is based upon key clinical randomized controlled trials and longitudinal studies published from 1992 through March, 1997 in the areas of diabetes, hypertension, lipid management, renal disease and foot and eye care. Each of the references listed have undergone a thorough review and rating based on the scientific rigor of the article, clinical relevance of the material presented and the ability to generalize using this data. Where existing literature is ambiguous or conflicting, or where scientific data are lacking on an issue, recommendations are based on the expert panels' opinion and clinical experience. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A letter, (e.g., "A or B") within a box of the algorithm refers the reader to an annotation for that box. The annotation typically follows the specific page of the algorithm in the sections labeled "Algorithms and Annotations" in each module. Strength of recommendations grading as well as level of evidence grading is based on AHCPR guideline development efforts[4]. For a description of each, refer to the following tables:

Strength of Recommendation[a]

Level I	Usually indicated, always acceptable and considered useful and effective.
Level IIa	Acceptable, of uncertain efficacy and may be controversial. Weight of evidence in favor of usefulness/efficacy.
Level IIb	Acceptable, of uncertain efficacy and may be controversial. May be helpful, not likely to be harmful.
Level III	Not acceptable, of uncertain efficacy and may be harmful. Does not appear in guidelines.

Strength of Evidence[b]

A	**B**	**C**	**D**
Primary Evidence	Randomized	Well designed clinical studies	Panel consensus
Secondary Evidence	Other Clinical studies	Clinical studies related to topic but not in a population with diabetes	Clinical studies Unrelated to topic

[a]From ACC/AHA Task Force Report
[b]AHCP classification.

The guideline and algorithm are designed to be adapted to the individual facility's needs and resources. The guidelines and algorithms will be updated as further research results become available. The ultimate goal is to improve local management of patients with diabetes and thereby improve patient outcomes.

GUIDELINE DEVELOPMENT

Diabetes in the Veterans Health Administration

Diabetes is now recognized to account for over 14% of health care expenditures in the United States, although only 3.1% of Americans have diagnosed diabetes.[4] The burden of diabetes in the VHA, documented in a recent series of VHA reports [6, 7, 8] is among the highest of any national health care system:

- The prevalence of diabetes among all veterans receiving outpatient care is estimated to be about 15%, and 20% among veterans receiving care in general medicine, primary care, or women's health clinics.

- The average demographic profile is that of a 64-year-old male with an income less than $7000.

- 12.0% of veterans were identified as having prescribed diabetes specific medications (insulin, oral agents, or monitoring supplies) as an outpatient in FY94. This group of veterans accounted for 24% of all pharmacy costs; nearly 7 cents out of every outpatient pharmacy dollar was spent on glycemic control medications and supplies. Given scientific advances since that time, the availability of new, and more expensive, antiglycemic agents; and a 40% increase in self-monitoring blood glucose (SMBG) expenditures, these data are considered to underestimate current expenditures.

- 28% of all veterans on dialysis in FY94 who received erythropoietin had an associated diagnosis of diabetes.

- 0.9% of veterans with diabetes sequentially examined in an Optometry Service multisite field study had severe visual loss

- 52% of all lower extremity amputations and revisions in the VHA in FY94 occurred in veterans with diabetes

- 5.6% of admissions of veterans with diabetes were associated with the metabolic complications of the disease, and 3.5% were for pneumonia or chronic obstructive pulmonary disease (COPD).

Although veterans with diabetes have a disproportionate number of hospitalizations relative to veterans without diabetes, diagnosis, education, preventive screening, risk factor reduction, and pharmaceutical treatment of diabetes, including microvascular and macrovascular complications, occurs mostly in the outpatient primary care setting.

However, despite the costs and morbidity associated with diabetes, and the general consensus that preventive care can delay, if not prevent, a significant percentage of the instances of visual loss, chronic renal failure, foot ulcers and lower extremity amputations, as well as admissions for metabolic control, 1996 baseline performance data from the VHA External Peer Review Program[8] indicates the following rates of preventive screening or intervention:

- 50.8% of veterans had at least an annual glycosylated hemoglobin test
- 46.5 % of veterans had an annual eye exam for the detection of retinopathy
- 71.8 % of veterans had an annual visual inspection of the foot
- 44.9% of veterans had an annual examination of pedal pulses
- 33.5% of veterans had an annual sensory examination of the foot
- 27.5% of veterans received an influenza vaccine
- 24.9% of veterans received a pneumococcal vaccine

Diabetes should be considered a serious public health problem both in the United States and in the Veterans Health Administration; and its detection and treatment must be viewed as the responsibility of all health care providers. Furthermore, although the primary care provider is responsible for overall coordination of care, each health care provider is urged to assume responsibility for ***preventive care*** for the ***entire person at time of each encounter***. For example, a podiatrist should be alert as to whether an eye exam has been performed within the past year; and an ophthalmologist should be concerned whether there is evidence of clinical nephropathy in a person with retinopathy. Each should be aware of the symptoms of uncontrolled hyperglycemia and be able to make appropriate referrals back to the primary care provider or subspecialist team. Expanded roles for nurse practitioners, nurses, physician assistants, dietitians and pharmacists should be considered.

These guidelines should be used as an impetus for administrators at each Veterans Integrated Services Network (VISN), facility, and care access site to develop innovative plans to break down the barriers preventing primary care providers, subspecialists and allied health professionals from working together, and from preventing patients from having prompt access to preventive care.

Guideline Development Process

The goal in developing the guideline for diabetes mellitus was not to repeat the guideline development process, but rather, to incorporate the information from several existing, national consensus, evidence-based guidelines into a format which would maximally facilitate clinical decision-making. The use of the algorithm format was chosen because of the evidence that such a format improves data collection, diagnostic and therapeutic decision-making and changes patterns of resource use. However, few guidelines are published in such a format. Furthermore, multiple guidelines covering the same topic, can be confusing and even conflicting. To enhance continuity of care, the VHA Diabetes Guidelines were designed to encompass a broad spectrum of outpatient care of patients with diabetes. This required incorporating multiple published guidelines into a single, unified document.

This guideline and the algorithms were the product of seven months of consensus building among over 70 experts from all aspects of the health care continuum. The list of developers/contributors include Veterans Health Administration professionals, senior representatives from key federal health related agencies including the Diabetes Division of the

National Institutes for Diabetes, Digestive and Kidney Diseases; Division of Diabetes Translation, Centers for Disease Control and Prevention; Office of Managed Care, Health Care Financing Administration; and the Pharmacoeconomic Center of the Department of Defense, as well as private sector experts provided by the VHA External Peer Review Program contractor. In addition, other participants hold or have recently held senior leadership positions in the American Diabetes Association, and the National Institutes of Health/Center for Disease Control and Prevention National Diabetes Education Program.

The list of contributors includes nurses, dietitians, social workers and physicians representing Podiatry, Endocrinology, Ophthalmology, Optometry, Geriatrics, Internal Medicine, and Primary Care and expert consultants in the field of guideline and algorithm development. Additionally, the guideline and algorithm draws heavily from existing American Diabetes Association, National Cholesterol Education Program, and National Kidney Foundation practice guidelines for diabetes mellitus. Recommendations for pharmacologic management of persons with diabetes, hypertension and hyperlipidemia developed by VHA's Medical Advisory Panel (MAP) to the Pharmacy Benefits Management Strategic Health Group are also integrated.

Consumer input is also being solicited and will be included in future revision of the guidelines. The results of these discussions, as well as insights from four focus groups with family members, will be instrumental in guiding future development of the algorithms. The perspective of the customers (veterans and their family members) is valued as a tool to help sensitize the algorithm developers and users to the needs of the patients.

In summary, it is acknowledged that the science and conclusions of other guidelines, especially those of the American Diabetes Association, have largely been incorporated into VHA guidelines. A summary of the VHA Diabetes Clinical Guidelines in relation to other existing national guidelines is provided in an attached table. However, the VHA Diabetes Guidelines represent the first comprehensive guidelines for this disease by a federal agency or national health care system in which risk stratification is both explicit and evidence based.

The VHA clinical guidelines are appropriate as a foundation, along with the use of the Pharmacy Benefits Management Strategic Health Group/Medical Advisory Panel Guidelines and Headquarters External Peer Review Program Performance Measures, for a Diabetes Chronic Disease State Management Program. Disease State Management can be defined as the continuous process of identifying and delivering, within selected patient populations, the most efficient combination of resources for the treatment of or prevention of disease. The rationale assumes that there are systematic ways health care delivery can be provided to a population that will be more efficient than the status quo. However, while the guidelines are appropriate for population based medicine, it is not their intent to prevent practitioners from using their best judgment in the care of an individual patient, but rather to establish verifiable treatment objectives for veterans with diabetes that will lead to a reduction in limb loss, visual loss, chronic renal insufficiency, and cardiovascular disease.

References:

1. AHCPR Clinical Practice Guideline, Number 5, Rockville, MD. US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication No. 93-0550, March, 1993

2. Optometry Service: Briefing to the Under Secretary for Health, 1995

3. Rubin RJ, Altman WM, Mendelson DN. Health Care Expenditures for People with Diabetes Mellitus, *JCEM* 78: 80-9A-F, 1992

4. The VA 1996 External Peer Review Program, Contract No. V101(93) P:1369

5. Veterans Administration National Center for Cost Containment Publications Diabetes Costs and Health outcomes in the VHA in FY94 (November, 1996)

6. VHA Directive 96-053, August 29, 1996. Roles and Definitions for Clinical Practice Guidelines and Clinical Pathways.

7. Wolfson M, Mundt D, Hawley G. Human Erythropoietin Utilization in the Department of Veterans Affairs Am J Kidney Disease 24:84-191, 1994

8. Woolf, SH. Practice guidelines, a new reality in medicine II. Methods of developing guidelines. *Arch Int Med* 1992 May;152: 947-48

9. Woolf, SH. Practice guidelines, a new reality in medicine III. Impact on patient care. *Arch Int Med* 1993 Dec;153:2647

COMPARISON OF VHA DIABETES CLINICAL GUIDELINES TO EXISTING NATIONAL DIABETES GUIDELINES

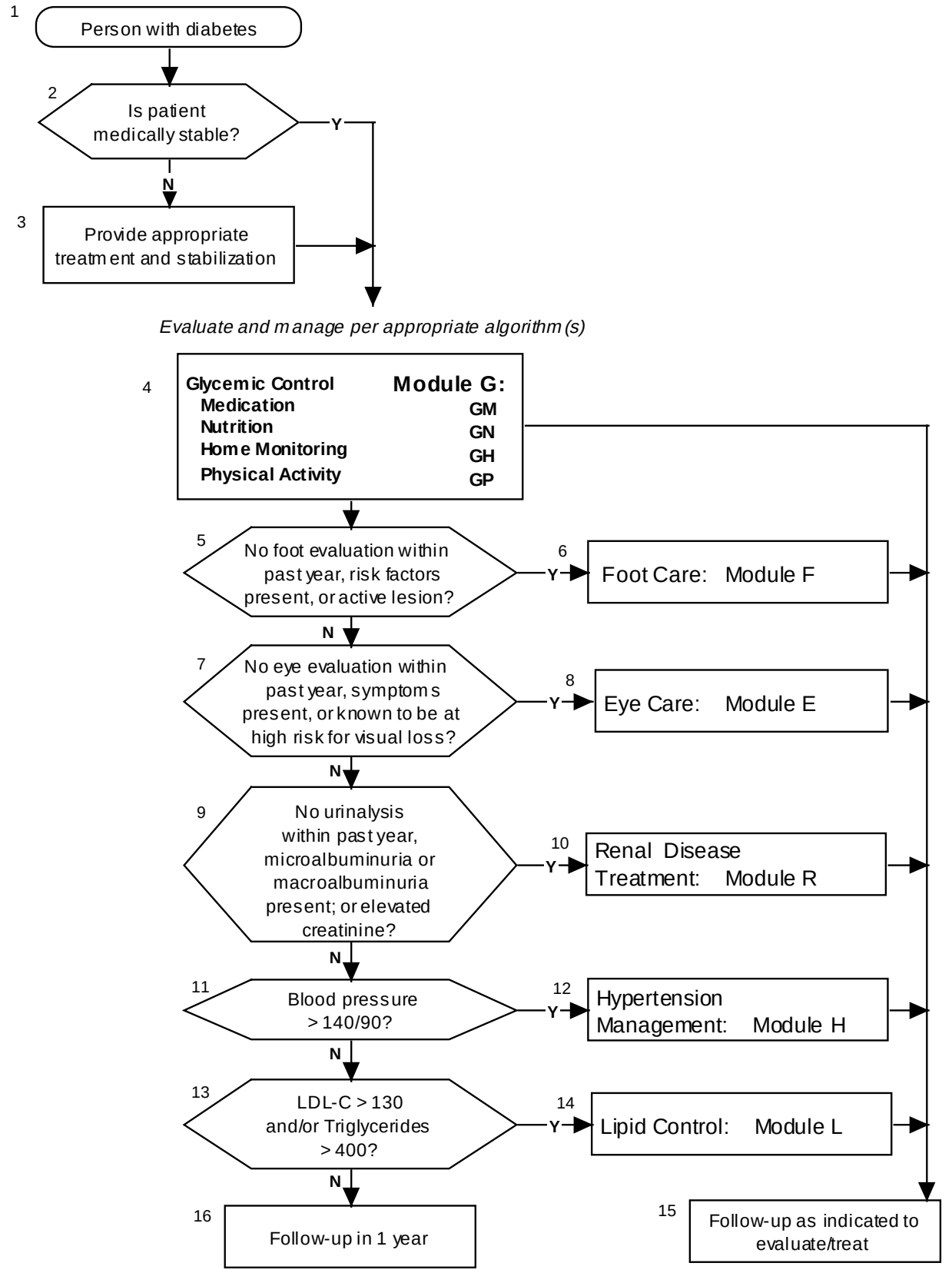
SUBJECT	EXISTING NATIONAL GUIDELINE	VHA GUIDELINE
Glycemic Control	**American Diabetes Association (ADA):** Recommended HbA_{1c} target ranges, with upper limit of normal 6%: < 7% (<1% above high normal range) Ideal. >8% (>2% above high normal range). Action suggested except in cases of diminished life expectancy.	HbA_{1c} target goals should be individualized and primarily based upon both life expectancy and presence or absence of microvascular complications. ≤ 7% (≤ 1% above high normal range) IF Life span 15 years or more in the absence of microvascular complications, OR 10 years of more in the presence of early to moderate microvascular disease. ≤ 8.0% (≤2% above high normal range) IF life span 5-15 years in the absence of microvascular disease, OR 5-10 years in the presence of microvascular disease. ≤ 9.0% (≤ above high normal range) IF life span less than 5 years, with or without macrovascular disease.
Self Monitoring of Blood Glucose	**ADA Consensus Statement:** Frequency of SMBG should be individualized according to clinical circumstances and response to treatment. Urine testing may be considered as an alternative if the only goal is avoidance of symptomatic hyperglycemia.	Frequency of SMBG should be individualized according to clinical circumstances and response to treatment. Urine testing may be considered as an alternative if the goal is avoidance of sympotmatic hyperglycemia. Explicitly recommends validation and documentation of user technique with prior to initial justification, and recommends assessment of whether individualized health outcome goals are met as part of ongoing interval justification.
Cholesterol	**National Cholesterol Education Program**: Goal is LDL-C<100 mg/dL for all persons with diabetes **American Diabetes Association:** Acceptable LDL-C<130 mg/dL for persons without coronary artery disease. and <100 mg/dL for persons with coronary artery disease. **American College of Physicians:** Screening for primary prevention is neither recommended nor discouraged between ages 65-75, and not recommended for individuals >75.	No upper age limit but does not recommend screening if life expectancy <5 years. Goal is LDL-C <130 mg/dL for all persons with diabetes. Consider LDL-C<100 mg/dL for persons with prior coronary artery bypass surgery.

COMPARISON OF VHA DIABETES CLINICAL GUIDELINES TO EXISTING NATIONAL DIABETES GUIDELINES

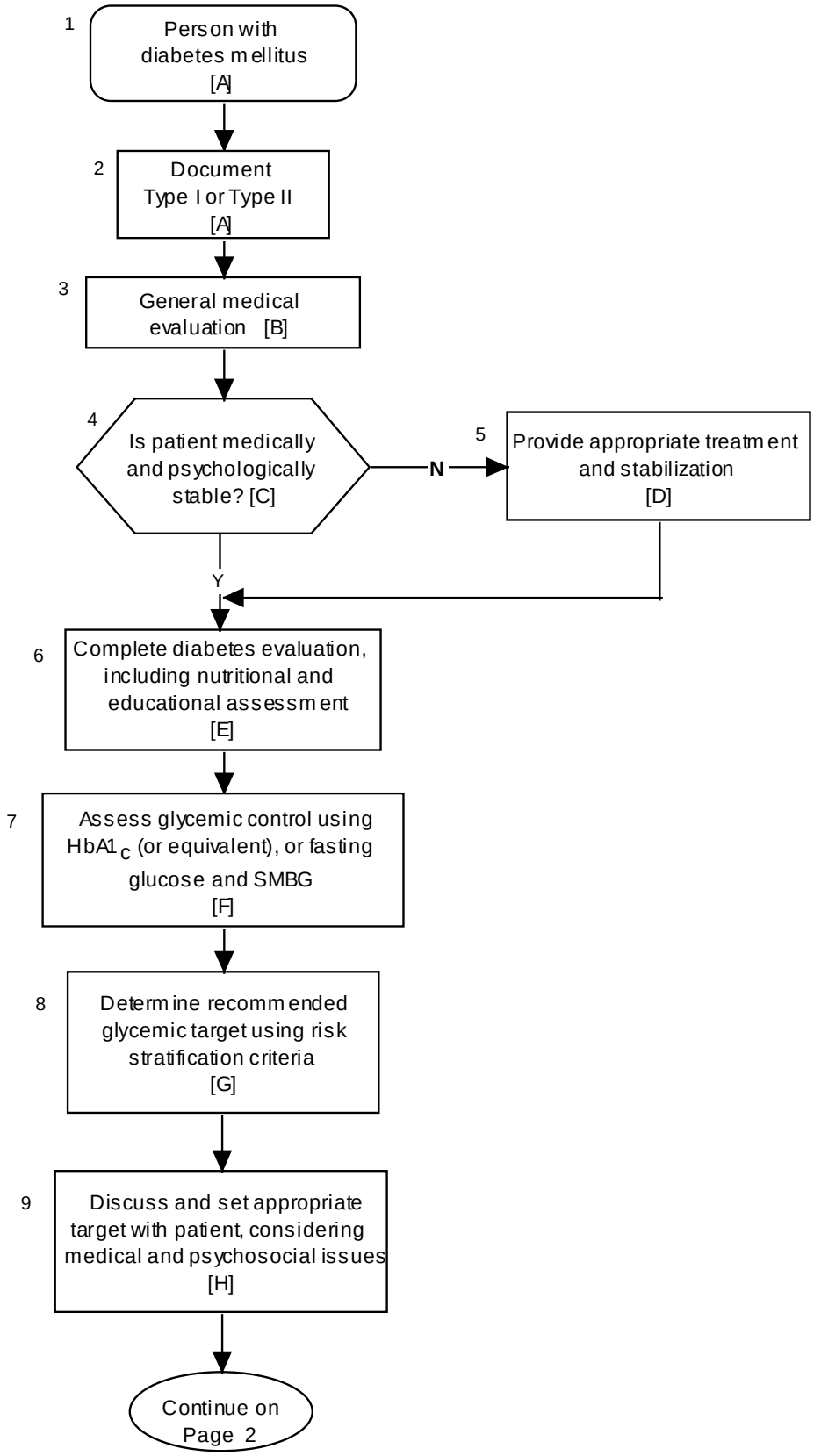
SUBJECT	EXISTING NATIONAL GUIDELINE	VHA GUIDELINE
Proteinuria	**National Kidney Foundation: No** screening after age 70; random urine specimen tested for albumin to creatinine ratio; scope of recommendations limited to screening for microalbumin; nephrology referral if albumin/creatinine ratio >300 mg/g or adverse effect of ACE inhibitor. **American Diabetes Association:** No upper age limit for screening; timed urine collection; urine specimen for albumin to creatinine ratio; or 24-hour specimen. Scope of recommendation includes proteinuria as well as microalbuminuria. Consider nephrology referral when GFR begins to decline substantially or creatinine >2.0.	No upper age limit but no screening for microalbuminuria if life expectancy <5 years: timed urine specimen preferred (24 hour or overnight) but random urine for albumin to creatinine ratio is acceptable. Scope of recommendations deals with elevated creatinine, proteinuria and microalbuminuria. Nephrology referral for creatinine >2.5 mg or 24 hour urine specimen for proteinuria >150 mg/L in the absence of any retinopathy (to evaluate for non-diabetic renal disease).
Eye Screening	**American Diabetes Association, American College of Physicians, American Academy of Family, Practitioners, American Optometric Association and American Academy of Ophthalmology:** Annual eye screening for persons with type I (Onset <30 years) diabetes mellitus >5 years (duration) or annually for individuals with type II diabetes. Acknowledges necessity for more frequent follow-up for retinal pathology.	Initial eye exam after 3-5 years duration for type I diabetes (onset <30 years). Annual eye screening if baseline or subsequent exam normal EXCEPT for persons with type II diabetes with HbA_{lc} <8.0% treated with oral agents who would be seen within 2 years if baseline or prior examination was normal. Individuals at "high risk" for visual loss are explicitly referred for case management by eye specialists.
Foot Screening	**American Diabetes Association:** Annual foot risk assessment, but without explicit stratification of risk factors.	Annual foot risk assessment, with high risk foot defined as presence of vascular insufficiency (absent pedal pulses, claudication or prior bypass surgery); insensate foot defined as inability to detect Semmes-Weinstien 5.07 monofilament at any site; foot deformity defined as hammer toes, claw toes and charcotgs foot; and prior ulcer/amputation.
Hypertension	**JNC-V: Systolic Diastolic** **Normal <130 <85** **High N1 130-139 85-89** **HTN >140 >90** American Diabetes Association: Defines hypertension as 140/90; however, the primary goal of therapy should be to decrease BP to <130/85.	Hypertension defined as >140/90. Acknowledges that other guidelines recommend that BP should be decreased to <130/85, but leaves goal of therapy to be individualized.

MODULE G: GLYCEMIC CONTROL

MANAGEMENT OF DIABETES MELLITUS



MANAGEMENT OF DIABETES MELLITUS
Glycemic Control



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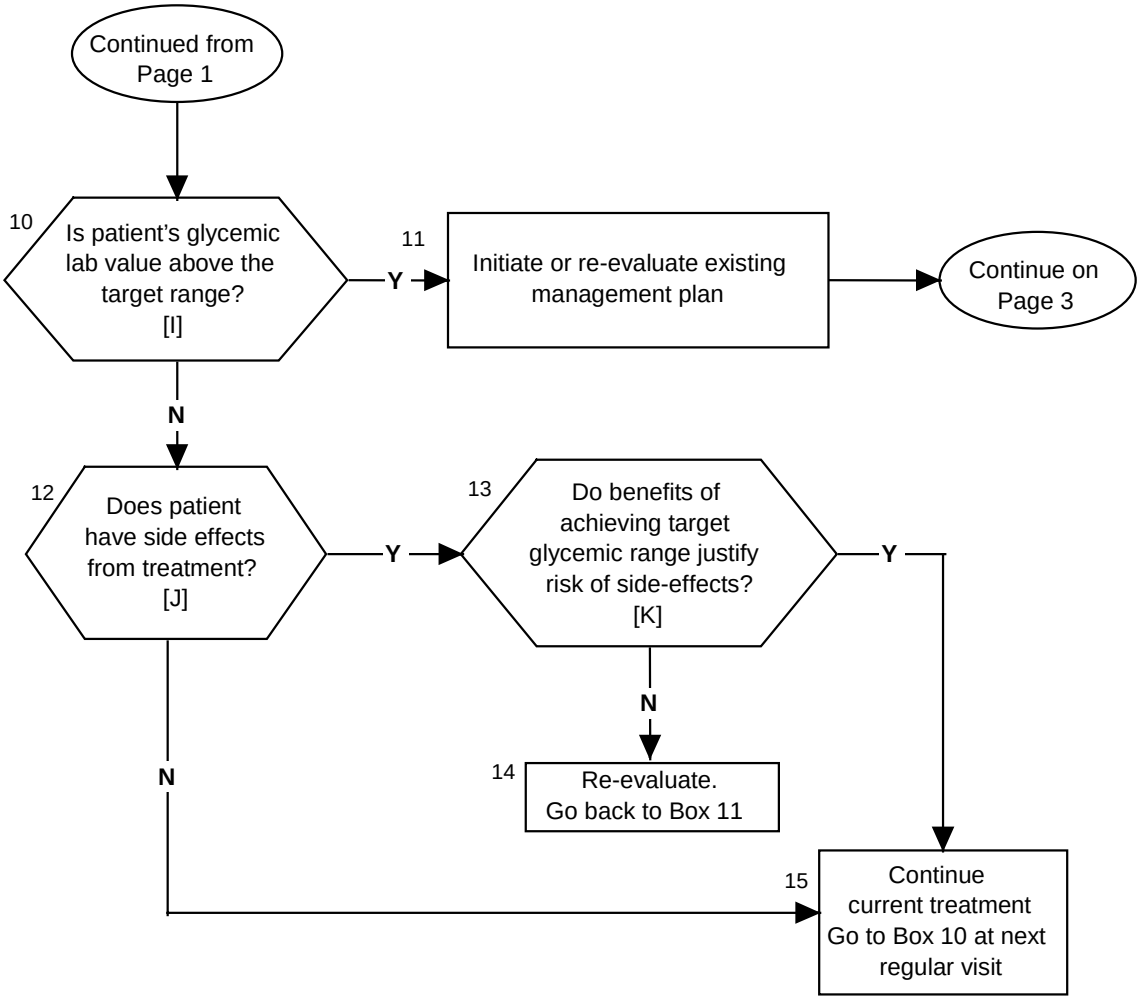
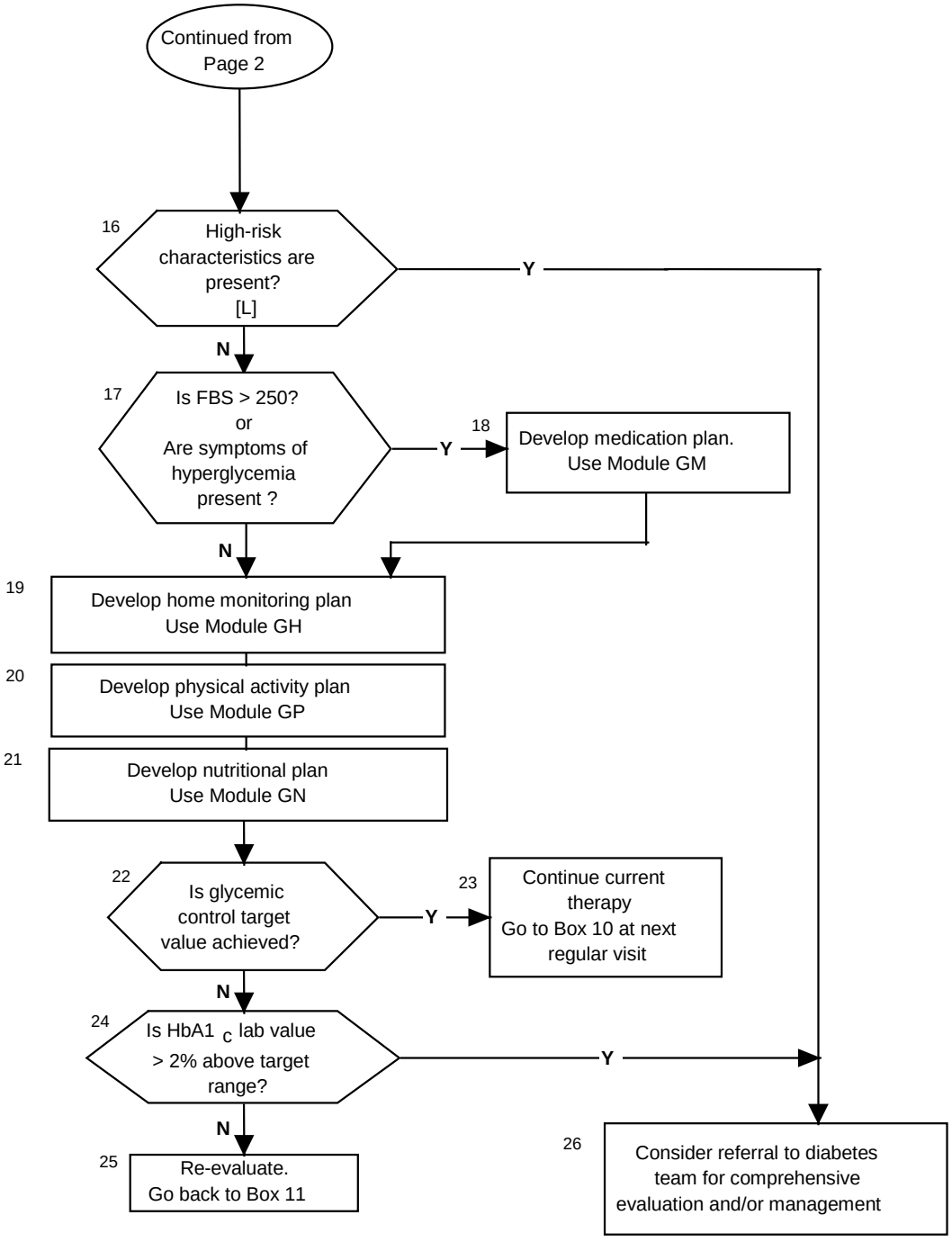


MANAGEMENT OF DIABETES MELLITUS
Glycemic Control



Module G:

Glycemic Control

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control Annotations

MODULE G

A. Patient Has Diabetes Mellitus

TABLE OF EVIDENCE

#	Factor	Reference	Strength of Recommendation	Level of Evidence
1	Blood Glucose Levels	Report of the Expert Committee on the Diagnosis & Classification of Diabetes Mellitus, June 1997	I	C

1. Biochemical Criteria for the Diagnosis of Diabetes

The criteria are derived from the *Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus* published June 1997. Oral glucose tolerance testing is not currently recommended for diagnosis in the general medical population. Variations in the accuracy and precision of glycosylated hemoglobin (HbA_{1c}) testing and capillary glucose monitoring measures (see Module G, Annotation F) preclude their use for diagnostic purposes. Patients with a random blood glucose level of > 200 mg/dL but without symptoms should have fasting blood glucose obtained and reevaluated.

DIAGNOSIS OF DIABETES

	TEST		
STAGE	Fasting Plasma Glucose (FPG) (Preferred) *	Casual Plasma Glucose	Oral Glucose Tolerance Test (OGTT)
Diabetes	FPG $\geq$ 126 mg/dl (7.0 mmol/l) **	Casual plasma glucose $\geq$ 200 mg/dl (11.1 mmol/l) plus symptoms ***	Two-hour plasma glucose (2hPG) $\geq$ 200 mg/dl ****
Impaired Glucose Homeostasis	Impaired Fasting Glucose (IFG) = FPG $\geq$ 110 and < 126 mg/dl		Impaired Glucose Tolerance (IGT) = 2hPG $\geq$ 140 and < 200 mg/dl
Normal	FPG < 110 mg/dl		2hPG < 140 mg/dl

*The FPG is the preferred test for diagnosis, but any one of the three listed is acceptable. In the absence of unequivocal hyperglycemia with acute metabolic decompensation, one of these three tests should be used on a different day to confirm diagnosis.
**Fasting is defined as no caloric intake for at least 8 hours.
***Casual = any time of day without regard to time since last meal; symptoms are the classic ones of polyuria, polydipsia, and unexplained weight loss.
****OGTT should be performed using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water. The OGTT is not recommended for routine clinical use.

Go Back

2. Clinical Classification of Type I or Type II

Patients with Type I diabetes are insulin requiring, and therefore will develop ketoacidosis if not treated with insulin, or if insulin requirements increase during stress. On the other hand, persons with Type II diabetes may need to be treated with insulin to improve glycemic control, but will usually not develop ketoacidosis if they do not receive insulin. Persons with diabetes treated with medical nutritional therapy (MNT), physical activity, and/or oral hypoglycemic or antiglycemic agents are classified as having Type II diabetes.

In practice, the proper diagnosis is important for several reasons. First, persons with Type II diabetes treated with insulin may be able to achieve comparable levels of glycemic control with hypoglycemic or antiglycemic agents, especially if they were placed on insulin because of an intercurrent illness, injury, or surgery and not subsequently reevaluated. Secondly, persons with Type I diabetes are generally more prone to develop hypoglycemia or ketosis, especially during times of stress.

For *coding purposes*, patients with Type I diabetes are coded as 250.01 or 250.03 (uncontrolled), while patients with Type II diabetes are coded as 250.00. or 250.02 (uncontrolled). Often the classification of diabetes was made at the time of diagnosis and never reevaluated. However, since persons with Type II diabetes can also present with a degree of ketosis, providers should be encouraged to review the classification of the diabetes in their patients.

In a primary care setting, determination of the patient's age at the diagnosis of diabetes, the *body mass index*, and urine ketones, is usually sufficient to classify the patient.

CLINICAL CLASSIFICATION

Classification	Likely Type I	Indeterminate	Likely Type II
Age	< 30	30-40	> 40
BMI	< 25	25-27	> 27
Urine ketones	moderate-large	small-moderate	negative-small

B. General Medical Evaluation — In the veteran population, diabetes may not be a patient's only disease, nor is it necessarily the disorder which needs to be prioritized for immediate treatment. It should also be noted that overt hyperglycemia is commonly precipitated by physical and psychological stress, and that *secondary forms* of diabetes, while rare, should be excluded.

C. Is Patient Medically and Psychologically Stable? — Urgent or semi-urgent medical conditions must be treated before chronic disease management principles are applied. "Stable" is the judgment of the individual provider. It should be noted that patients with diabetes who have more immediate medical or psychiatric problems should still have an *educational needs assessment* done to determine whether they have sufficient skills to

manage their glycemic control during a period of intercurrent illness, with a goal of avoiding symptomatic hypo- or hyperglycemia.

D. Provide Treatment and Stabilization — Any numerical metabolic criteria for admission for persons with significant hypo- or hyperglycemia are arbitrary. *INTERQUAL* criteria are widely used in the Veterans Health Administration. However, it should be noted that the criteria are *not* risk stratified for co-morbid conditions, socioeconomic circumstances, or psychological status. Furthermore, factors such as proximity to the provider or the availability of telephone monitoring are *not* included in the criteria. Therefore, the decision for hospitalization versus outpatient treatment must be consistent with the provider's best judgment.

E. Complete Diabetes Evaluation, Including Nutritional and Educational Assessment

1. History (Emphasize the following in patients with diabetes)

    a. Hyperglycemia
        - Onset of hyperglycemic symptoms
        - Date of diagnosis of diabetes
        - Manner of presentation
            - Asymptomatic/routine blood test
            - Polyuria/polydipsia
            - Ketoacidosis
            - Hyperosmolar syndrome
        - Treatment history
            - Initial
                - Pharmacologic (oral agent vs insulin, dosage, frequency and duration of therapy)
                - Nutrition therapy
                - Physical activity
            - Current/Align
                - Nutritional/physical activity;
                - pharmacologic (dosage, frequency, *timing to meals and activity*)
                - Recurrent symptoms of hyperglycemia (polyuria, polydypsia, blurred vision)

    b. Hypoglycemia
        - Frequency, time of day, relation to meals or exercise
        - Severity (coma, seizure, mode of therapy)
        - *Symptoms*

    c. Nutrition
        - Weight history*
        - Current meal plan

    d. Lifestyle
        - Exercise/activity*
        - ETOH*

* indicates External Peer Review Program Chronic Disease Process Measure

- Smoking*
- Substance use
- Occupation

e. Glucose monitoring*
- Urine/blood
- Frequency
- *Assessment of competency*
- Monitor is used
- How are results reported? To whom?
- Actions taken as a result of readings

f. Complications: specific history
- Infections (recent vs. past history)
  - GU
  - Skin
  - Sinus/middle ear
  - Foot (see nerve, peripheral vascular disease)
    - osteomyelitis
    - cellulitis
- Dental
- Immunizations (influenza and pneumococcal)*
- Eye (current status vs. past history)
  - Cataract
  - Glaucoma
  - Photocoagulation
  - Change in vision
  - Date of last (dilated) eye exam by specialist
- Foot
  - Pain/paresthesia
  - Ulcer
  - Joint
  - Amputation
- Kidney
  - Blood pressure
  - Proteinuria (micro or macro)
  - History of elevated creatinine
- Peripheral vascular
  - Claudication
  - Poor healing
  - Amputation
- Coronary heart disease
  - Smoking
  - Family history
  - Hypertension
  - Cholesterol (total, HDL and/or LDL)
  - Triglycerides
  - Angina
  - MI

* indicates External Peer Review Program Chronic Disease Process Measure

Arrhythmia
CHF
Cerebral vascular disease
TIA
CVA

2. Physical Examination (Emphasize the following in patients with Diabetes)

   a. Consider *secondary etiologies* (Cushing's, acromegaly, hemochromatoses, medications)

   b. Weight, height, *body mass index* (BMI is calculated by dividing the patient's weight in kg by the patient's height, in meters, squared. Metric conversions are pounds divided by 2.2=kg; inches x 0.0254=meters*)*

   c. *Dilated eye exam (annual or as indicated) See Module E*

   d. Oral exam (dental and gingival health)

   e. Cardiovascular system: heart, peripheral circulation including pulses and bruits

   f. Skin: infections, xanthoma, insulin injection sites

   g. Peripheral vascular: claudication, poor healing, and amputation

   h. Coronary heart disease risk factors: smoking, family history, hypertension, cholesterol (total, HDL and/or LDL), triglycerides, angina, MI, arrhythmia, and CHF

   i. Cerebral vascular disease: TIA and/or CVA

   j. Feet: visual* (including nails, web spaces, ulcers, calluses, *deformities*), palpation of pulses* and sensation* (consider use of a 5.07 monofilament; Call Project LEAP, Carville LA 504-642-4714 for information on vendors)

   k. Neurological system: sensory state of hands and feet, interosseous muscle wasting, DTRs

F. Assess Glycemic Control Using HbA_{1c}* (or Equivalent) or Fasting Glucose and SMBG — Although blood glucose, fructosamine, and glycosylated hemoglobin levels can be used together to assess immediate, short term and long term glycemic control, glycosylated hemoglobin performed or reported as hemoglobin HbA_{1c} is the only laboratory test validated in controlled randomized clinical trials as a predictor of risk for

* indicates External Peer Review Program Chronic Disease Process Measure

microvascular complications. If mean blood glucose levels are accurately determined and known, then they can be used to estimate hemoglobin HbA_{1c} levels.

TABLE OF EVIDENCE

FACTOR: USE OF HbA_{1c} LEVELS AS A RISK FACTOR FOR DEVELOPMENT OF MICROVASCULAR DISEASE

#	Factor	Reference	Strength of Recommendation	Level of Evidence
1	Validation of HbA_{1c} testing	DCCT Research Group 1993	I	A
		Ohkubo et al. (1994)		
		DCCT Research Group 1995;	I	A
		1996	I	A

The assessment of glycemic control in an individual requires an understanding of the methods used to assess long term blood sugar control (*glycosylated hemoglobins*); short term glycemic control (*fructosamine);* and single point measurement of blood sugar (venous samples and capillary glucose measurements). The key points to remember are that you must determine the method and accuracy of the glycosylated hemoglobin test performed in the laboratory at your facility, how the results are reported, and what the high normal cutoff value is. You should be able to obtain this information from the Chief of Laboratory Service or a diabetologist. Since there is inherent error in the test, you should realize that the reported value has a range of error associated with it. Ideally, your laboratory should participate in a standardization program for glycosylated hemoglobin testing that results in accuracy within 5% as recommended by the American Diabetes Association (ADA), The National Institutes of Health, and the American Association of Clinical Chemists. In addition, either a HbA_{1c} test should be performed or the results of the glycosylated hemoglobin assay should be reported as HbA_{1c} equivalents. Finally, while venous blood sugars are accurate and standardized throughout the VHA, "capillary measurements" can vary widely. Detailed explanations follow.

GLYCOSYLATED HEMOGLOBIN

1. The terms "glycated" and "glycosylated" hemoglobin are used interchangeably in the literature. The terms are used to describe the reaction product between sugar and a protein.

2. Glycosylated hemoglobins (GHb) are most useful for monitoring diabetic patients.

3. There are four HbA_1 components: HbA_{1a1}, HbA_{1a2}, HbA_{1b}, HbA_{1c}.

4. The Scientific Research Group of the Diabetes Control and Complication Trial (DCCT) and the ADA recommend HbA_{1c} as the marker of choice for the assessment of risk for the development of microvascular complications, as well as for monitoring glycemic control.

5. Risk assessment of secondary complications stratified to level of glycemic control will be based on the HbA_{1c} database of the DCCT, which was standardized for accuracy by a "gold standard" or peer consensus reference method.

6. Facilities that measure total GHb should be able to provide accurate HbA_{1c} equivalency values. However, there is no analytic system that measures HbA_1 and can report HbA_{1c} equivalency values.

7. Some methods are more susceptible to hemoglobinopathy (i.e., Hb S, C, D, G, F, and labile intermediate products) interference that can cause biases in the test results. In order to obtain accurate HbA_{1c} values it is important to assay specimens with known hemoglobinopathies on analytic systems that are insensitive to hemoglobin variants as interfering substances. Presently, only one analyzer (HPLC method using borate-affinity column chromatography) can be used reliably for this purpose. If a patient has a hemoglobinopathy, consult with the Laboratory Chief to determine whether or not the glycosylated hemoglobin test performed at your institution is valid for that particular patient.

8. HbA_{1c} measurements may also be unreliable in the presence of the following conditions: hemolytic anemia, uremia, or pregnancy. Serum fructosamine measurement may be considered as an alternative test in these circumstances.

SERUM FRUCTOSAMINE MEASUREMENT

1. Fructosamine is a glycosylated protein that may be a potential marker for assessment for glycemic control for the 10-20 days prior to measurement.

2. Newer assays appear to be highly specific for fructosamine and free from interference by urates and triglycerides. The assay has a limitation, i.e., that gross changes in protein concentration and half-life may have large effects on the proportion of protein that is glycosylated. Thus, results obtained may be invalid in the presence of cirrhosis of the liver, nephrotic syndrome, dysproteinemias, or rapid changes in acute-phase reactants.

GLUCOSE MEASUREMENTS

Practical uses of glucose measurements:

1. Self-Monitoring of Blood Glucose (SMBG) or point of care glucose measurements should not be substituted for the laboratory glucose measurement for the diagnosis of diabetes mellitus.

2. HbA_{1c} or its equivalent is the only validated indicator for assessment of risk for microvascular complications.

3. The most common user error associated with SMBG is inadequate sample size. Depending upon the meter used, this error can lead to a significant discrepancy between the actual and recorded blood glucose. A user's technique and maintenance procedures should be reviewed annually or as indicated.

4. The accuracy and precision of the glucose meter should be determined (see Blood Glucose Monitoring Devices Resource Guide, from the VA National Center for Laboratory Accuracy and Standardization, published February 1997).

5. Assuming that the mean SMBG or point of care or laboratory glucose measurements are accurate, multiple readings at various time points can be averaged to obtain approximate HbA_{1c} levels by using the equation from the DCCT database:

6.

MEAN BLOOD GLUCOSE	ESTIMATED HbA_{1c}
120 mg/dL Glucose =	6% HbA_{1c}
150 mg/dL Glucose =	7% HbA_{1c}
180 mg/dL Glucose =	8% HbA_{1c}
Every 30 mg/dL increase =	1% increase

G. Determine Recommended Glycemic Target Using Risk Stratification Criteria — The upper limit of normal HbA_{1c} is approximately 6% in the absence of diabetes. For persons with diabetes mellitus, it is recommended that the current American Diabetes Association recommendation that the ideal HbA_{1c} goal is 7%, with therapeutic action suggested at values > 8% be individualized through a risk stratification approach based upon an understanding of the interaction among glycemic control (HbA_{1c} level), duration of diabetes (life expectancy), presence or absence of microvascular complications, family history, and ethnicity. Using this approach, target levels would range between 7% and 9%.

≤ 7.0% (≤ 1% above high normal range): Life expectancy of 15 years or more in the absence of diabetic complications, or 10 years or more in the presence of early to moderate microvascular disease.

≤ 8.0% (≤ 2% above high normal range): Life expectancy of 5-15 years in the absence of microvascular disease, or 5-10 years in the presence of microvascular disease.

≤ 9.0% (≤ 3% above high normal range): Life expectancy of less than 5 years, with or without microvascular disease.

TABLE OF EVIDENCE
INTERVENTION: LEVEL OF GLYCEMIC CONTROL
DEVELOPMENT AND PROGRESSION OF RETINOPATHY

#	Variable	Reference	Strength of Recommendation	Level of Evidence
1	progression to non-proliferative retinopathy	DCCT Research Group 1993	I	A
		Ohkubo et al. (1995)	I	A
		DCCT Research Group 1995	I	A
2	progression to proliferative retinopathy	DCCT Research Group 1993	I	A
		Ohkabo et al. (1995)	I	A
3	progression to blindness	Klein R et al. (1994)	I	B

TABLE OF EVIDENCE
DEVELOPMENT AND PROGRESSION OF NEPHROPATHY

#	Variable	Reference	Strength of Recommendation	Level of Evidence
1	progression to microalbuminuria	DCCT Research Group 1993	I	A
		Ohkubo et al. (1995)	I	A
		DCCT Research Group 1995	I	A
		Krolewski 1995	I	B
		Kawazu et al. (1994)	I	A
2	progression to proteinuria	DCCT Research Group 1993	I	A
		Ohkubo et al. (1995)	I	A
3	progression to end stage renal disease	DCCT Research Group 1993	I	C
		Ohkubo et al. (1995)	I	C
		Klein R et al. (1995)	I	C

TABLE OF EVIDENCE
DEVELOPMENT AND PROGRESSION OF NEUROPATHY/AMPUTATIONS

#	Variable	Reference	Strength of Recommendation	Level of Evidence
1	progression to neuropathy	DCCT Research Group 1993	I	A
		DCCT 1995	I	A
2	progression to amputations	Klein et al. (1995)	I	B
		Mayfield et al. (1996)	I	B

TABLE OF EVIDENCE
PREVENTION OF CARDIOVASCULAR DISEASE

#	Variable	Reference	Strength of Recommendation	Level of Evidence
1	myocardial infarction, stroke	DCCT Research Group 1993	IIb	A
		Ohkubo et al. (1995)	IIb	A
		Anderson et al. (1995)	IIb	B
		Singer et al. (1992)	IIb	B
		Abraira et al. (1997)	IIb	A
		Klein et al. (1995)	IIb	B

TABLE OF EVIDENCE
FACTOR: LIFE EXPECTANCY

#	Risk Factor	Reference	Strength of Recommendation	Level of Evidence
1	Effect of diabetes on life expectancy	Panzram et al. (1981)	I	B
		Marks 1975	I	B
		Goodkin 1975	I	B
		Singer 1992	I	B
2	duration of diabetes and incidence of end stage microvascular complications	Klein R et al. (1995)	I	B
		Klein R et al. (1994)	I	B
		Palmberg P et al. (1981)	I	B
		United Kingdom prospective diabetes study (UKPDS) 1995	I	A
		Humphrey et al. (1989)	I	B

TABLE OF EVIDENCE
FACTOR: ETHNICITY

#	Factor	Reference	Strength of Recommendation	Level of Evidence
1	Effect of ethnicity on glycemic target levels	Haffner et al. (1988)	IIa	B
		Hamman et al. (1989)	IIa	B
		Lee et al. (1992)	IIa	B
		Nelson et al. (1988)	IIa	B
		Rabb et al. (1990)	IIa	B
		Cruickshanks et al. (1987)	IIa	B
		Arfken et al. (1994)	IIa	B
		Cowie et al. (1989)	IIa	B
		Burden 1992	IIa	B
		Stephens et al. (1990)	IIa	B

TABLE OF EVIDENCE
FACTOR: PRE-EXISTING MICROVASCULAR DISEASE

#	Variable	Reference	Strength of Recommendation	Level of Evidence
1	pre-existing retinopathy or	DCCT Research Group 1993	I	A
	microalbuminuria as	Ohkubo et al. (1994)	I	A
	a risk factor for progression	DCCT Research Group 1995	I	A

RISK STRATIFICATION OF GLYCEMIC TARGET RANGES

1. Estimate the life expectancy of the person you are treating.

Statistics for the life expectancy of a population can be derived from the observed mortality rates of that population. An example commonly used in medicine would be the life expectancy of persons with a particular type and stage of cancer. The population would have an average survival, with a wider range of survival into which almost all individuals would fall. While it would be impossible to tell an individual person exactly how long he or she would live, it would be possible to provide that person with some estimate of his or her life expectancy. Based upon life expectancy and mortality rates due to the disease, the provider and patient would discuss treatment options. Prostate cancer would be a specific example of how this concept could be used.

Longitudinal studies of the life expectancy of persons with diabetes have been done and indicate that persons with diabetes have a shortened life span relative to persons without diabetes. However, the format of the data from such studies is not easily utilized. To provide the clinician with a means of estimating life expectancy for populations of men and women with Type II diabetes, tables (See Exhibits G1 and G2) have been generated based upon a computer model (courtesy Richard Eastman, MD, NIDDK; Eastman et al. Diabetes Care, 1997), that incorporates data from the Framingham Study. Except for end stage renal disease, the model assumes that microvascular complications do not affect survival, although they do predict progression to blindness, amputation, and dialysis.

Co-existing conditions (such as CHF, AIDS, COPD, cirrhosis, cancer, etc.) have a significant effect on survival, but are not explicitly noted in the tables. However, for any given age at the time of diagnosis of diabetes, the years of life remaining after diagnosis are provided in the 25th, 50th, 75th, and 95th percentiles. It can be assumed that populations of persons with diabetes and other health conditions would have a survival rate less than the mean life expectancy (use 25th percentile), and that persons without co-morbid conditions and with a favorable family history would have a survival rate greater than the mean life expectancy (use 75th or 95th percentile).

Furthermore, aggressive treatment of cardiovascular risk factors (see Lipid and Hypertension modules), including smoking cessation, may increase life expectancy. In addition, adherence to general preventive practices (for example immunizations, screening for colon, prostate, and breast cancers) is also predicted to increase life expectancy in the American population.

Thus, for an individual with diabetes, an estimate of life expectancy for a given percentile can be obtained by determining the person's age at the time of diagnosis of diabetes and determining the average (mean) years of life remaining by subtracting the time (in years) that has elapsed from the time of diagnosis. Providers must then use their best judgment to raise or lower it based upon coexisting medical conditions and family history.

While a person's age is clearly the predominant factor in estimating life expectancy, this approach ensures that the life expectancy estimate used in determining target glycemic ranges for an individual is also based upon the person's individual health state and the best judgment of the clinician.

2. *Determine the presence or absence of early to moderate retinopathy and diabetic nephropathy* (see Renal and Eye Modules).

The presence of microvascular complications (e.g., retinopathy, microalbuminuria, neuropathy) increases the probability that end stage microvascular complications (e.g., visual loss, renal failure, and amputation) will occur as compared to the probability for an individual without microvascular complications but with a similar life expectancy.

3. *Consider genetic factors.*

The risk stratification approach can be extended by the practitioner to include family history of microvascular complications. Results from the DCCT and other studies indicate that a familial history of diabetic nephropathy or retinopathy does predispose a sibling or a child towards developing microvascular complications. However, the evidence does not support different treatment goals for individuals of varying ethnicity's. While the prevalence of diabetes and its complications is higher in ethnic populations, the increase in microvascular complications cannot be attributed to an increased sensitivity to the effects of hyperglycemia.

4. *Determine an initial target value of glycosylated hemoglobin based upon consideration of the patient's life expectancy, presence of microvascular complications, and genetic factors.*

Based upon the DCCT results, using an HbA_{1c} value obtained by HPLC with an intra-assay variation of 0.1% and a high normal value of 6.05%, the following target levels are recommended as starting points for negotiation with the patient.

≤ 7.0% (1% above high normal range): Life expectancy of 15 years or more in the absence of diabetic complications or 10 years or more in the presence of early to moderate microvascular disease.

≤ 8.0% (2% above high normal range): Life expectancy between 5 and 15 years in the absence of microvascular disease, or between 5 and 10 years in the presence of microvascular disease.

≤ 9.0% (3% above high normal range): Life expectancy of less than 5 years, with or without microvascular disease.

NOTE: Risk stratification should be based upon glycosylated hemoglobin results performed or reported as HbA_{1c} values. Depending upon the glycosylated hemoglobin assay used at your facility, the absolute value of the target range may differ from the DCCT recommendations, although the percent (%) above high normal value will not.

5. *Negotiate the target range with the patient, taking into account risks and benefits of the proposed therapeutic intervention (see Annotation H).*

Providers must recognize that a target range of glycosylated hemoglobin, based upon life expectancy, microvascular complications, and familial history, is a starting point for negotiation with the patient. It does not mean that a lower HbA_{1c} level will not be beneficial, nor does it mean that the provider and patient should not negotiate a lower one. Rather, it implies that there is a decreasing benefit from achieving improved glycemic control, which should be taken into account when evaluating the risks and benefits of pharmacologic therapy as well as patient preferences. Also, it should be recognized that reduction in risk from decreasing HbA_{1c} is a continuum, so a negotiated "target level" does not have to be exactly 7.0, 8.0, or 9.0. A detailed explanation of the terms absolute risk reduction and relative risk reduction follows.

RELATIVE AND ABSOLUTE RISK REDUCTION

Based on the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and DCCT findings, the major determinants of the effectiveness of glycemic control in preventing the development or progression of clinically significant (e.g., visual loss, renal insufficiency, and amputation) complications are: (1) the patient's life expectancy and, (2) the presence of earlier microvascular disease, especially retinopathy, persistent microalbuminuria or macroproteinuria (See Eye Module) when other conditions have been excluded (see Renal Module) and peripheral neuropathy (see Routine Care Foot Module).

The Ohkubo Study was a controlled randomized trial that demonstrated that intensive insulin therapy in Japanese individuals with Type II diabetes who were

not overweight had similar results to the DCCT with respect to reduction in the onset and progression of retinopathy and microalbuminuria.

Analysis of the risk reduction in microvascular complications from the DCCT supports the conclusion that the *relative risk reduction* of intermediate microvascular complications of diabetes (i.e., development of background retinopathy and microalbuminuria) can be reduced by about 40% for each 1% decrease in HbA_{1c} in persons with Type I diabetes.

Although controlled, randomized trials of glycemic control in Type II individuals who are overweight or from other ethnic groups are not available, longitudinal population studies (WESDR) demonstrate that the exponential rise in the risk of retinopathy in persons with Type II diabetes follows a similar gradient as for persons with Type I diabetes. Consequently, the evidence is consistent with the conclusion that the development of microvascular disease is similarly related to glycemic control in persons with either Type I or Type II diabetes.

However, it should be noted that the conclusions of the DCCT and Ohkubo studies were based on intermediate microvascular complications. Progression to proliferative retinopathy was uncommon, and no patients progressed to renal insufficiency. Therefore, it should be recognized that maximal benefits of glycemic control in preventing the progression of microvascular disease to the endpoints of visual loss or chronic renal insufficiency accrue over a period of time longer than that of the study period of the aforementioned trials.

Thus, the probability that an individual with diabetes will develop these complications is based upon his or her life expectancy. However, the mean age at onset of Type II diabetes (> 50 years of age) is greater than that for Type I diabetes. Consequently, life expectancy from the time of diagnosis is lower in persons with Type II diabetes as a result of death from cardiovascular conditions as well as all other causes (co-morbidity).

There are no interventional trials that conclusively demonstrate that improved glycemic control will alter cardiovascular morbidity and/or mortality. The DCCT and the Ohkubo trials show a nonsignificant trend towards reduced cardiovascular events with intensive insulin therapy, while the VA Cooperative trial demonstrates a nonsignificant increase in cardiovascular events and an association between decreased HbA_{1c} and new cardiovascular events. Observational studies demonstrate an association between increased HbA_{1c} and cardiovascular disease and cardiovascular mortality risk that achieves statistical significance only for women.

For populations of persons with diabetes, it is possible to estimate the decrease in microvascular complications that would result from improved glycemic control. Absolute risk reduction is defined as the decrease in visual loss (blindness), end stage renal disease, or amputation that occurs with a given decrease in percent HbA_{1c}. Since the previously noted clinical studies are limited in duration, computer models of Type I and Type II diabetes have been developed that can

provide estimates of the incidence of microvascular complications and life expectancy. These models provide population estimates of risk, and can be useful in providing both providers and persons with diabetes with an estimate of risk over time as well as an estimate of benefit from improved glycemic control.

In conclusion, the *absolute risk reduction in endstage microvascular disease over an individual's lifetime* is the major determinant of the target range of glycemic control for an individual, and will influence the risk/benefit analysis of therapeutic options.

H. Discuss and Set An Appropriate Target with the Patient, Considering Medical and Psychosocial Issues — It is evident that the risks of therapy are different for each individual, dependent upon his or her medical, social, and psychological status. Thus, the risks of a proposed therapy must be balanced against the potential benefits. Factors for the provider and person with diabetes to consider in jointly making this decision should include the following:

- Appropriate medical support and psychosocial environment
- History of severe, recurrent hypoglycemia
- The possible consequence of adverse effects associated with hypoglycemia (consider cardiovasular disease, anticoagulation, use of dangerous equipment, etc.)
- Alcohol or substance abuse
- The presence of multiple end-stage microvascular complications, including macular edema, proliferative retinopathy and macroproteinuria, especially with elevated serum creatinine.
- Pregnancy, or the intention to become pregnant
- Symptomatic cardiovascular disease
- Willingness and ability to self-monitor and to make appropriate life-style change
- Quality of life
- Specific risks of individual therapeutic options

I. Is Glycemic Control, by Lab Value, Above the Target Range? — Since there is no evidence to suggest that the frequency of obtaining glycosylated hemoglobin levels is correlated with improvement in that level in Type II diabetes, practitioners must use their own judgment in deciding upon frequency in an individual patient. Factors to be considered include whether glycemic control is stable; whether the target goal has been achieved; and whether therapy has been changed. An assessment of long term, short

term, and current glycemic control can be made by integrating information obtained from glycosylated hemoglobin levels, fructosamine values, and serum/capillary glucose measurements (see annotation F).

J. **Does the Patient Have Side Effects from Treatment? —** Side effects can include hypoglycemia and specific complications from oral agents. Patients with hypoglycemia should be evaluated for precipitating factors that may be easily correctable (missed meals, incorrect administration of insulin [dosage or timing], exercise, etc). In many cases a simple adjustment can be made in nutrition, exercise, medication and/or patient self monitoring (see Nutrition, Physical Activity, Medication, and Home Monitoring sub-algorithms). In persons with near normal glycemic control (most specifically persons with Type I diabetes on intensive insulin treatment; or in persons with autonomic neuropathy), it may be necessary to relax the degree of glycemic control, at least temporarily. Complex adjustments may best be accomplished through co-management with a Diabetes Team.

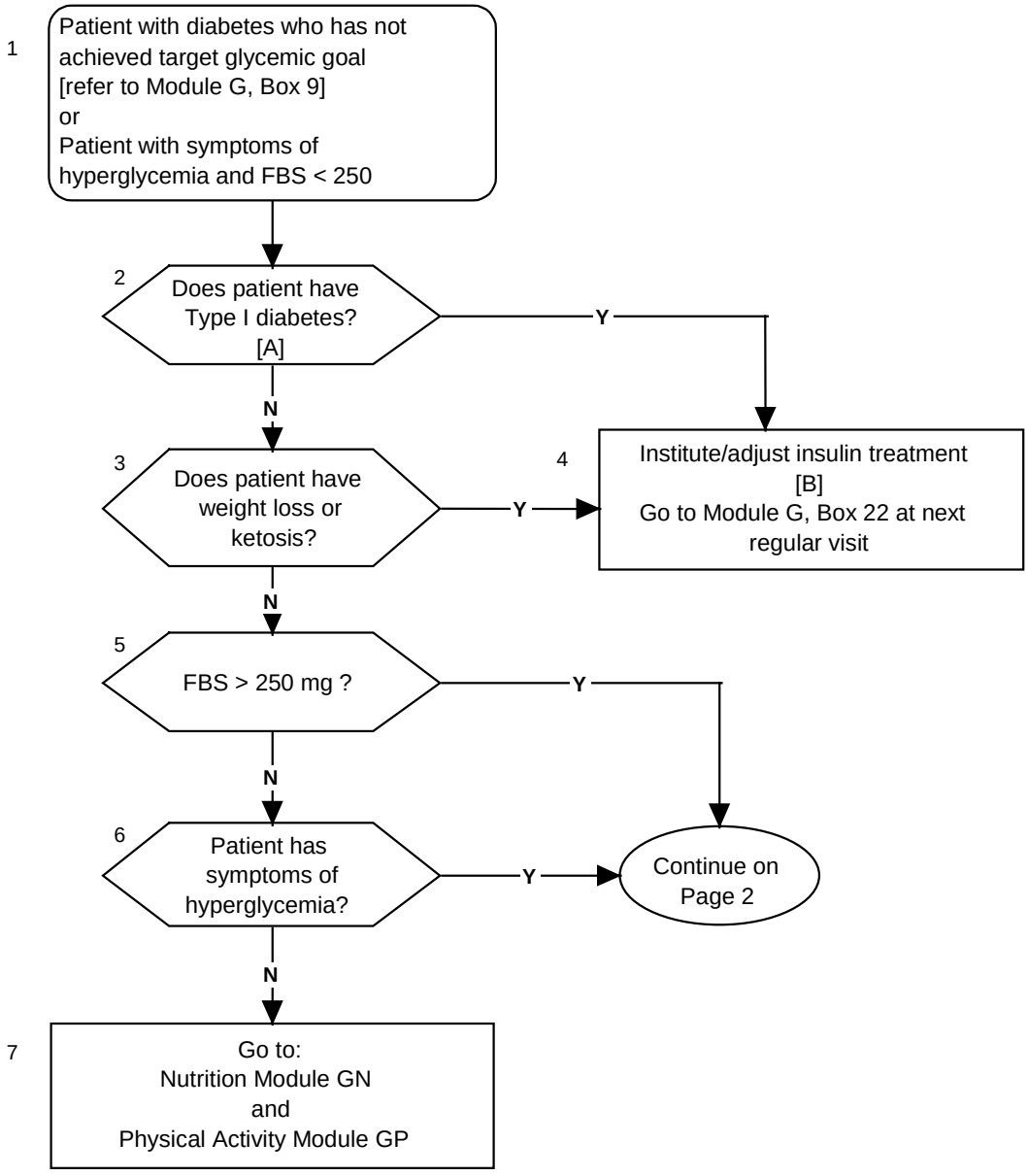
K. **Do the Benefits of Achieving Target Glycemic Range Justify the Risk of Side Effects? —** With the exception of pregnancy, where glycemic control affects the health of the baby and the mother, the benefits and risks of therapy are related to reduction in absolute risk of end stage complications for the individual. In that context, the occurrence of severe hypoglycemic reactions in a young person with Type I diabetes on an intensive insulin regimen has a different context than in an older individual with known coronary artery disease. Decisions on risk/benefit are always individual. It must also be recognized that steps can be taken to reduce the incidence of side effects of therapy (especially hypoglycemia; see Annotation J).

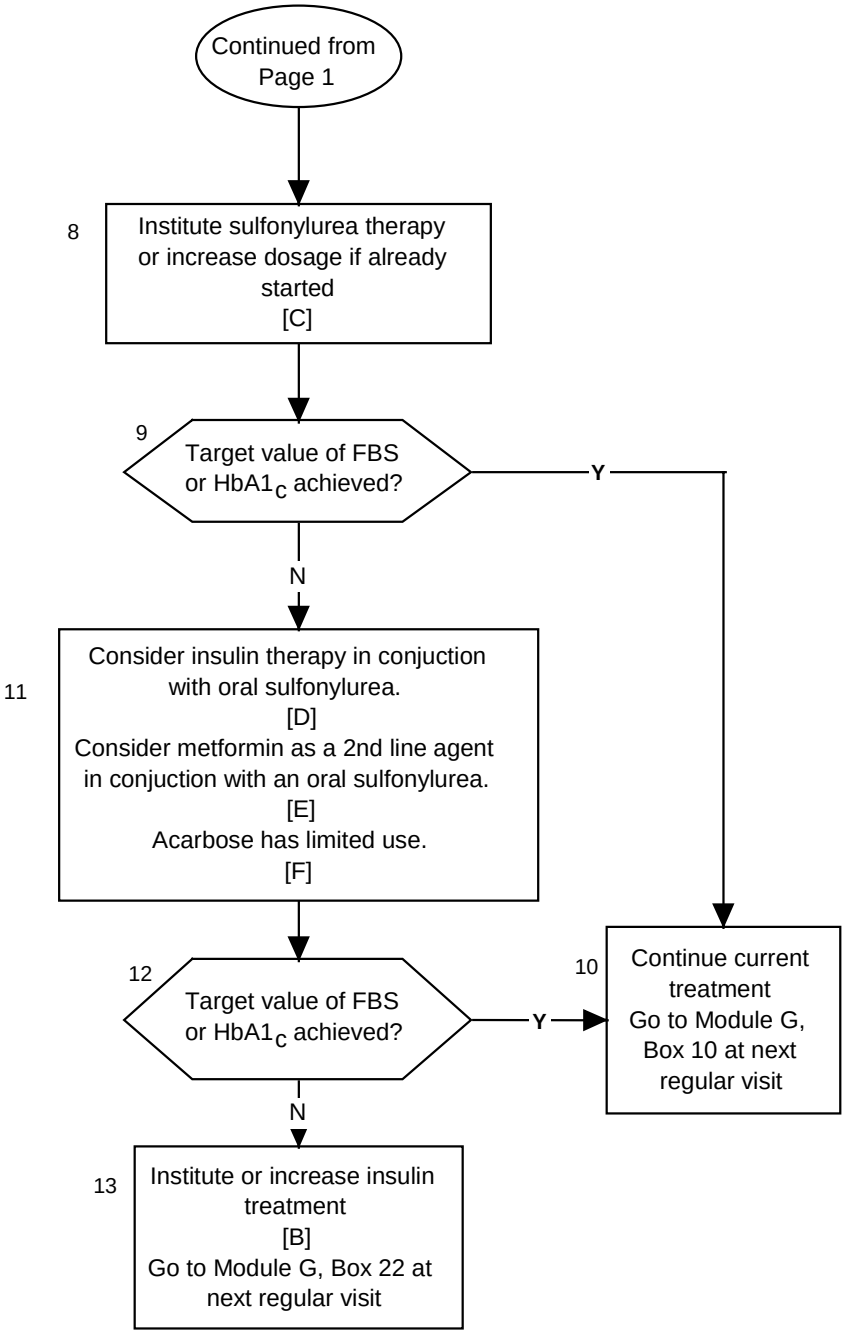
L. **Are High Risk Characteristics Present? —** Patient is pregnant or is planning pregnancy; is on an intensive insulin regimen; has recurrent or severe hypoglycemia, has hypoglycemic unawareness; or has had recent hospitalizations for DKA or severe hyperglycemia.

MODULE GM:

GLYCEMIC CONTROL: Medication

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control: Medication




Continued from Page 1
8
Institute sulfonylurea therapy or increase dosage if already started
[C]
9
Target value of FBS or HbA1c achieved?
Y
N
11
Consider insulin therapy in conjuction with oral sulfonylurea.
[D]
Consider metformin as a 2nd line agent in conjuction with an oral sulfonylurea.
[E]
Acarbose has limited use.
[F]
12
Target value of FBS or HbA1c achieved?
Y
10
Continue current treatment
Go to Module G, Box 10 at next regular visit
N
13
Institute or increase insulin treatment
[B]
Go to Module G, Box 22 at next regular visit

Module GM

Glycemic Control: Medication

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control: Medication Initiation Or Adjustment Annotation

MODULE GM

A. Does Patient Have Type I Diabetes?—In a primary care setting determination of the patient's age at the diagnosis of diabeties, the body mass index, and urine ketones is usually sufficient to classify the patient.

CLINICAL CLASSIFICATION

Classification	Likely Type I	Indeterminate	Likely Type II
Age	< 30	30-40	> 40
BMI	< 25	25-27	> 27
urine ketones	moderate-large	small-moderate	negative-small

B. Institute/Adjust Insulin Treatment—Types, frequency and dosages of insulin must be individualized. Factors to be considered are: Type I or Type II diabetes; age; weight; comorbid conditions; presence of autonomic neuropathy; concomitant medications (specifically beta blockers); patient ability to perform self glucose monitoring and inject insulin accurately; risks and benefits of hypoglycemia, including psycho-social factors; and magnitude and pattern of hyperglycemia.

Type I Diabetes

Insulin dosages vary widely among patients, even when other factors are similar. For persons with new onset Type I diabetes, it is recommended that initial therapy be individualized in consultation with a Diabetes Team.

The dosages could then be increased by 2-6 units depending on body weight and glucose levels at the appropriate times. Persons with Type I diabetes are, in general, more sensitive to changes in insulin dosage and far more susceptible to episodes of hypoglycemia than individuals with Type II diabetes. In persons with Type I diabetes treated on intensive insulin regimens the risk of severe hypoglycemic reactions was increased by 300% in the context of a resource intensive controlled randomized trial (DCCT). Such individuals should be managed in collaboration with a Diabetes Team. For all patients, adjustments are best made in conjunction with SMBG (refer to Module GH) in the patient's normal environment.

Type II Diabetes

Many patients with Type II diabetes can achieve target glycemic levels with bedtime insulin, a single injection of insulin, or split mixed insulin. Some individuals with Type II diabetes, as well as individuals with Type I diabetes, will need intensive insulin treatment to achieve near normal glycemic target goals. For these individuals regimens may include a short acting insulin before meals with Ultralente before breakfast and/or bedtime; intermediate and short acting insulin before breakfast, with short acting insulin

before dinner and an intermediate bedtime insulin. For individuals with Type II diabetes, an American Diabetes Association publication notes that a safe way to begin insulin is to start with an arbitrary dose and increase it gradually until the desired level of control is achieved. For lean persons (< 125% ideal body weight) a total dose of 15 units, with 2/3 before breakfast and 1/3 before dinner, could be recommended; in obese patients (> 125% ideal body weight) the dose could be doubled. Again, individual risks and benefits must be addressed.

In persons with Type II diabetes the VA Cooperative Study demonstrated that HbA_{1c} results similar to the DCCT trial can be obtained in the veteran population, with no increase in weight and with minimal episodes of severe hypoglycemia. However, this again was in the context of a resource intensive controlled trial with a subspecialty team, and it is recommended that such individuals also be comanaged in collaboration with a Diabetes Team.

COMPARISON OF INSULIN PREPARATIONS[a-c]

*The following tables are from the VA, Medical Advisory Panel (MAP) Pharmacologic Management of Non-Insulin Dependent Diabetes Mellitus (NIDDM)

INSULIN[a]	ONSET (HRS)	PEAK (HRS)	DURATION (HRS)	APPEARANCE
Regular	0.5-1	2-4	5-7	clear
NPH	1-2	6-14	24+	cloudy
Lente	1-3	6-14	24+	cloudy
Ultralente	6	18-24	36+	cloudy
Lispro	10-15 minutes	30-90 minutes	4	clear

[a]Adapted from Koda-Kimble MA. Diabetes Mellitus. In: Koda-Kimble MA, Young LY eds. Applied Therapeutics: The Clinical Use of Drugs. 5th ed. Vancouver: Applied Therapeutics Inc., 1992:72-10.
[b] Package insert. Humalog (insulin lispro). Indianapolis, IN: Eli Lilly and Company, 1996.
[c]Onset, peak, and duration are parameters for non-human insulin preparations; in general, human preparations have shorter times of duration

INSULIN REGIMEN EXAMPLES[a-c]
***From VA Medical Advisory Panel**

Once-Daily Morning NPH Insulin	Appropriate for elderly or non-compliant patients Inject 30-60 minutes before breakfast Usual dosage < 40 units/day
Split Mixed Regimen with NPH/Regular	Inject 2/3 of the total insulin requirement in the morning, with a NPH/Regular ratio of 70/30 Inject 1/3 of the total insulin requirement in the evening, with a NPH/Regular ratio of 50/50[b]
Bedtime Dosing of NPH or Lente Insulin in Addition to an Oral Agent	Begin with 10-15 units at bedtime Example: A dose equal to the morning glucose/18[c] Verify that the pre-dinner glucose remains in control

[a]Adapted from Edelman SV, White d, Henry RR. Intensive insulin therapy for patients with Type II diabetes. Current opinion in endocrinology and diabetes 1995;2:333-340.
[b] These are a few examples, optimal regimen depends on the individual patient
[c] Always counsel patients to mix regular insulin in syringe first, followed by NPH. Lente insulin should not be mixed with Regular insulin

General Guidelines for Insulin Adjustment in the NIDDM Patient

- If the morning FBS is off target, adjust the evening NPH or switch evening NPH to bedtime
- If the evening BS is off target, adjust the morning NPH
- If the evening glucose continues to be off target, have the patient check the pre-lunch glucose
- If the pre-lunch glucose is off target, adjust the morning Regular insulin
- If the bedtime glucose is off target, adjust the evening Regular insulin

Selected Costs for NIDDM Drug Therapy (as of November 1996)
***From VA Medical Advisory Panel**

For current prices, check the Drug Product Management bulletin board at (708) 531-7947

DRUG	USUAL DOSE[a]	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
Oral Sulfonylureas		
1st generation		
Chlorpropamide	250 mg qd	$ 0.60
Tolazamide	250 mg bid	$ 2.82
Tolbutamide	500 mg bid	$ 0.90
2nd generation		
Glimeripide	4 mg qd	$ 25.80
Glipizide[b]	10 mg bid	$ 1.77
Glyburide[b]	5 mg bid	$ 4.02

DRUG	USUAL DOSE[a]	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
Insulin		
Lente Human - U100/10mL	individualized	$ 5.10 / vial
Lispro Human - U100/10mL	individualized	$ 15.58 / vial
NPH Human - U100/10mL	individualized	$ 5.10 / vial
Regular Human - U100/10mL	individualized	$ 5.10 / vial
Ultralente Human - U100/10mL	individualized	$ 5.33 / vial
70/30 Human - NPH/Regular 10mLl	individualized	$ 5.10 / vial
Metformin	850 mg bid	$ 29.18
Acarbose	50 mg tid	$ 25.60

[a]Usual dose; does not reflect equivalent doses
[b]National contract

C. Institute Sulfonylurea Therapy or Increase Dosage if Already Started[1]

1. Initiation or adjust oral agents — No difference in long term efficacy or failure rate has been demonstrated among the different sulfonylureas. The average maximum decrease in HbA_{1c} for these agents is 2%. Approximately 15% of patients may never achieve adequate glucose control (primary failure) and 5-10% per annum lose control of blood glucose (secondary failure). Pharmacologic differences in sulfonylureas may have important clinical implications, particularly with regard to iatrogenic hypoglycemia.

TABLE OF EVIDENCE
INTERVENTION: POTENCY OF ANTIGLYCEMIC AGENTS COMPARED TO SULFONYLUREA THERAPY

Intervention	Reference	Strength of Recommendation	Level of Evidence
Metformin	United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 12, 1995	I	A
Acarbose	Coniff 1995	I	A

2. On sulfonylurea therapy, institute sulfonylurea therapy, increase dosage.

***From VA Medical Advisory Panel**

First-line agent	A second generation oral sulfonylurea is the first-line agent, based on safety. HbA_{1c} should be measured 3-6 months after changes in therapy
Alternate first-line agent	A first-generation sulfonylurea can be used as an alternate agent. Chlorpropamide should only be used in patients < 65 years old who are already on it and stable; it should not be used as a new agent

Oral Sulfonylureas[a,b*]
***From VA Medical Advisory Panel**

Sulfonylurea	Potency	Dosing Interval	Daily dose (mg/day)	Plasma half-life (hrs)	Duration Of Action (hrs)	Active Metabolites
First Generation						
Chlorpropamide	Low	qd	100-750	24-48	24-72	yes
Tolazamide	Low	qd-bid	100-1000	4-7	12-24	yes
Tolbutamide	Low	bid-tid	500-3000	4-8	6-12	no
Second Generation						
Glimepiride	High	qd	1-8	9	≥24	yes
Glipizide	High	qd-bid	5-40	1-5	≥24	no
Glipizide XL	High	qd	5-20	2-5	≥24	no
Glyburide	High	qd-bid	2.5-20	10-16	≥24	weak

[a]Adapted from Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. Drug Safety 1994; 11:223-241.
[b]Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,1996:129a-130u.

[1] VHA PMB-MAP. The Pharmacologic Management of Non-Insulin Dependent Diabetes Mellitus. VHA PHB-SHG Publication No. 96-004. Hines, IL: Pharmacy Benefits Management Strategic Health Group. December 1996.

Drugs that Potentiate Sulfonylurea Action[a,b]
***From VA Medical Advisory Panel**

DRUGS	MECHANISM
Acarbose, alcohol, monoamine oxidase inhibitors, metformin, salicylates	Intrinsic hypoglycemic activity
Chloramphenicol, monoamine oxidase inhibitors, warfarin	Decreased hepatic metabolism
Clofibrate, salicylates, sulfonamides, warfarin	Displacement from plasma protein[c]
Probenecid, salicylates	Decreased renal excretion

[a]Adapted from Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. Drug Safety 1994;11:223-241.
[b]Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,1996:129a-130u.
[c]Clinical significance disputed

D. Consider Insulin Therapy in Conjunction with an Oral Sulfonylurea[2] — In patients failing a maximal dose of sulfonylurea therapy, many patients can be convinced to start bedtime insulin daytime sulfonylurea (BIDS) because only one injection and one SMBG before breakfast are required. If the target glycemic level is not achieved, then the use of multiple dosages of insulin should be considered. For lean individuals, especially if elderly, 5-10 units of NPH insulin would be an appropriate range for starting bedtime insulin, while 10-15 units can be recommended for obese individuals. Doses of insulin are best adjusted according to SMBG results obtained in the patient's usual environment.

E. Consider Metformin as Second Line Agent

1. Recommendation — Use as a second-line oral agent (in combination with an oral sulfonylurea at maximum dosage) in the event of oral sulfonylurea failure. The effect of metformin on glycemic control should be additive, due to its different mechanism of action.

2. Efficacy in lowering HbA_{1c} is comparable to oral sulfonylureas; the average maximum decrease in HbA_{1c} is 2%.

3. Does not result in weight gain.

4. A reduction in plasma triglycerides may occur.

5. The patient should be advised of the transient, dose-related GI side effects (diarrhea, nausea, vomiting, bloating, flatulence, anorexia).

7. Discontinue if testing of glycemic control fails to show improvement over 3 months.

[2] VHA PMB-MAP. The Pharmacologic Management of Non-Insulin Dependent Diabetes Mellitus. VHA PMB-SHG Publicatoin No. 96-004. Hines, IL: Pharmacy Benefits Management Strategic Health Group. December 1996.

***From VA Medical Advisory Panel**

DOSE	CAUTIONS/MONITOR
• Check S_{cr} and LFTs prior to starting therapy • Start 500-850 mg q am with meals • ↑ dosage as needed by 500-850 mg every 2 weeks (split dose bid) • The usual maintenance dose is 850 mg bid with meals • Maximum dose: 2550 mg/day	• Inform patient to take with food to avoid possible GI symptoms (diarrhea, nausea, vomiting, bloating, flatulence, anorexia) • Counsel patient to be aware of possible metallic taste in mouth • Monitor BUN, creatinine, and electrolytes within 2 weeks of initiation or dosage change • Lactic acidosis, ↑ incidence with: — S_{cr} > 1.5 mg/dL (male) or > 1.4 mg/dL (female) — Abnormal hepatic function — Presence of acute or chronic acidosis (e.g. severe sepsis) — Evidence of acute or chronic tissue hypoxia (e.g. COPD, CHF, acute MI) — Recent history of alcoholism — Contrast media radiographic studies (48 hrs before or after) • Avoid use with alcohol • Cimetidine, furosemide and nifedipine may increase metformin concentrations

[a] Adapted from Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,1996:129a-30u.

F. Acarbose Has Limited Use

1. Recommendation — Due to its side-effect profile, multiple daily dosing regimen, and lower efficacy, this agent has limited indications.

2. Local medication use guidelines should be developed. Suggestions for utilization:

   (a) Inadequately controlled patients (2% above HbA_{1c} goal) who are unable to take sulfonylureas and/or metformin (allergies, adverse reactions, contraindications). The effect of acarbose on glycemic control should be additive, due to its different mechanism of action;

   (b) Patients inadequately controlled on sulfonylurea and metformin combination therapy, after discontinuation of metformin if the patient did not respond. The addition of acarbose is used to avoid insulin therapy (although this may potentiate the hypoglycemic potential of these agents);

   (c) Patients with elevated postprandial BS, or impaired glucose tolerance.

3. Its efficacy in lowering HbA_{1c} is inferior to that of the oral sulfonylureas and metformin; the general maximum reduction in HbA_{1c} is 0.5 - 1.0 %.

4. Refer to Medical Advisory Panel Table below for contraindications to the use of acarbose.

5. The patient should be advised of the transient, dose-related GI side effects (diarrhea, abdominal pain, flatulence).

6. A reduction in plasma triglycerides may occur.

7. Discontinue if failure to show improvement in glycemic control over 3-6 months.

Acarbose Drug Therapy[a,b*]
***From VA Medical Advisory Panel**

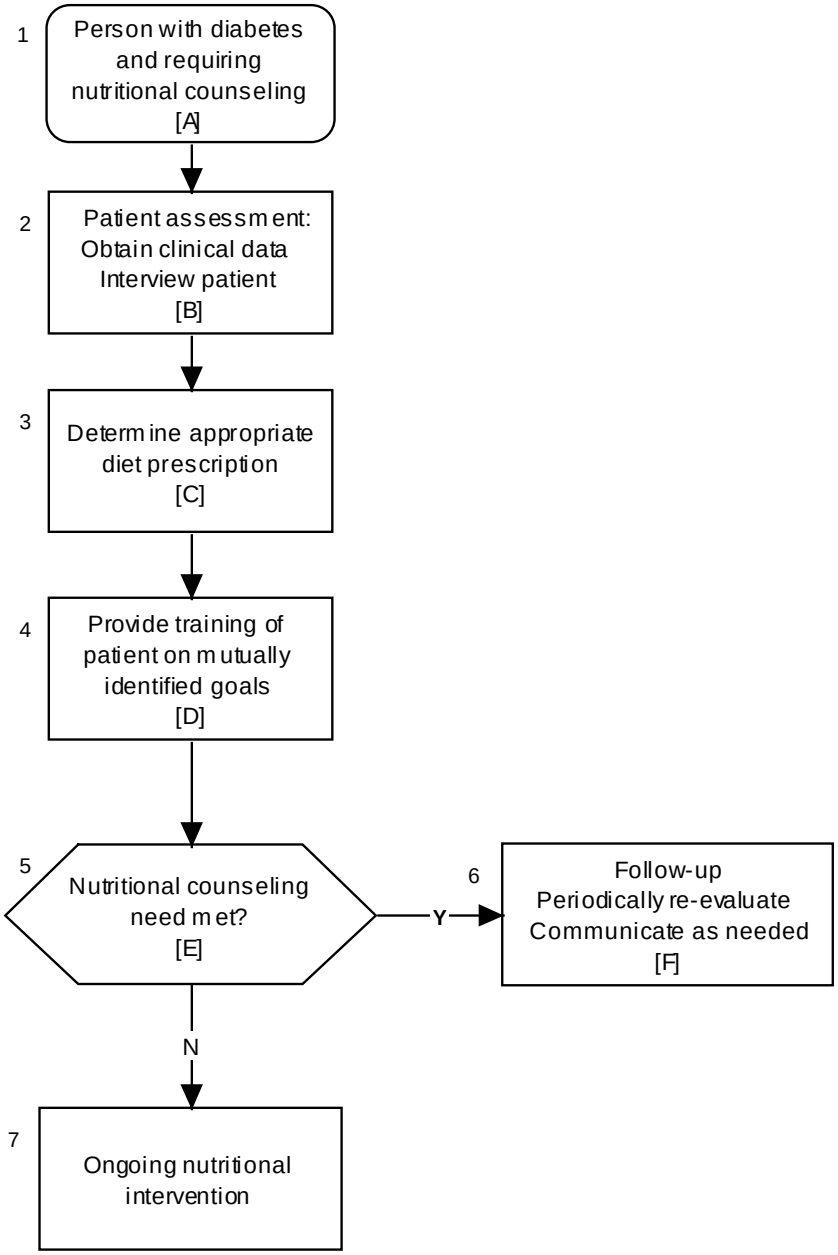
DOSE	CAUTIONS/MONITOR	CONTRAINDICATIONS
25 mg tid[c]	• Inform patient to take dose with the first bite of each main meal • Patients should maintain a diet high in complex carbohydrates and low in simple sugars to achieve maximum benefit and minimize adverse effects • Inform patient of possible GI symptoms (e.g., diarrhea, abdominal pain, flatulence) that may occur during the first few weeks of therapy • Monitor serum AST/ALT levels every 3 months during the first year of treatment • Renal impairment has been shown to increase plasma concentrations of acarbose; its use is not recommended in these patients	• Hypersensitivity to the drug • Presence of diabetic ketoacidosis or cirrhosis • Presence of intestinal complications (e.g., ulcerations, obstructions, digestion or absorption disorders)

[a]Adapted from Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc.,1996:129a-129e.
[b]Martin AE, Montgomery PA. Acarbose: An a-glucosidase inhibitor. Am J Health-Syst Pharm. 1996;53:2277-90.
[c]This is the recommended starting dose. Dosing must be individualized on the basis of both effectiveness and tolerance not to exceed max. of 100 mg tid

MODULE GN

GLYCEMIC CONTROL: Nutrition

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control: Nutrition



Module GN

Glycemic Control: Nutrition

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control: Nutrition

Module GN

A. Person with Diabetes Requiring Nutritional Counseling — Medical nutrition therapy and exercise are the initial treatments for diabetes mellitus. A three-month trial is appropriate unless fasting blood sugar > 250 mg% or for patients who have a fasting blood sugar < 250 mg% with symptoms of hyperglycemia. Newly-diagnosed patients, patients whose diabetes is judged out of control, patients using insulin pumps or multiple daily injections, and patients with serious nutrition-related complications should be referred for individualized assessment and instruction in meal planning. Frequent nutritional counseling may be indicated for such patients.

B. Patient Assessment

1. Clinical data: current height/weight and BMI

2. Nutrition history: usual food intake and pattern of intake; energy and macronutrient composition; weight history, appetite, and digestion problems; frequency and choices of restaurant meals; alcohol intake; vitamin, mineral, or nutrient supplement use

3. Exercise pattern: type of activity/exercise, frequency, duration, and motivation

4. Psychosocial and economic issues: living situation, cooking facilities, ability to obtain and prepare food, finances, educational background, employment, ethnic or religious belief considerations, literacy, family support, need for food assistance if applicable (e.g., Meals on Wheels, food banks)

5. Glucose monitoring: knowledge of target blood glucose ranges, glucose testing method, frequency of testing, blood glucose records, and use of data from monitoring

6. Knowledge/readiness to learn basic food/meal planning, attitude

7. Smoking history: present pattern, cessation or participation in smoking cessation program

C. Determine Appropriate Diet Prescription — Based upon consideration of whether the patient has Type I or II diabetes, the target glycemic goal, and the information obtained from the patient assessment, an appropriate diet prescription will be negotiated.

D. Provide Training of Patient on Mutually Identified Goals

Note: Topics to be covered during the initial therapy of 3 or 4 visits.

1. Risk factors associated with diabetes

2. Role and effect of nutrition, exercise, medication, weight loss/maintenance, and smoking or blood glucose management

3. Definitions: examples of carbohydrate, protein, and fat

4. Nutrition prescription:

    - Calories based on individual needs and goals; initiate plan to achieve reasonable weight

    - Fats: restrict according to risk factors and severity of serum lipid levels

    - Carbohydrates: based on nutrition assessment

5. Meal planning and timing of meals

6. How to maintain a food intake record and its importance to treatment

7. Recognition and treatment of hypoglycemia

8. Sick day management

9. Targeting of blood glucose levels, self-monitoring of blood glucose, and measures to take based on monitoring

10. Use of food labels and shopping skills

11. Dining out

12. Recipe modification; portion sizes

13. Long-term management goals: target blood glucose levels and glycosylated HbA_{1c}, weight, lipids, blood pressure, lifestyle change, medication regimen

14. Insulin regimen, onset, peak, and duration; impact of food and activity on glucose level

    Goals are:

    - Achievement and maintenance of appropriate blood glucose and glycosylated hemoglobin levels by balancing food intake with insulin and/or oral hypoglycemic or antiglycemic agent and activity levels.
    - Achievement of optimal serum lipid levels (see Lipid Algorithm).
    - Provision of adequate energy for maintaining reasonable weight.
    - Appropriate medical nutrition therapy for acute and chronic complications such as hypoglycemia, short-term illness, autonomic neuropathy, hypertension, cardiovascular disease, renal disease.
    - Improvement of overall health.

E. Nutritional Counseling Met — For patients with a specific need, such as (but not limited to) pregnancy, brittle diabetes, hypoglycemic reactions, failure to achieve target goal, evaluation to discontinue insulin, etc., ongoing (and frequent) nutritional counseling may be appropriate to achieve a specific health goal.

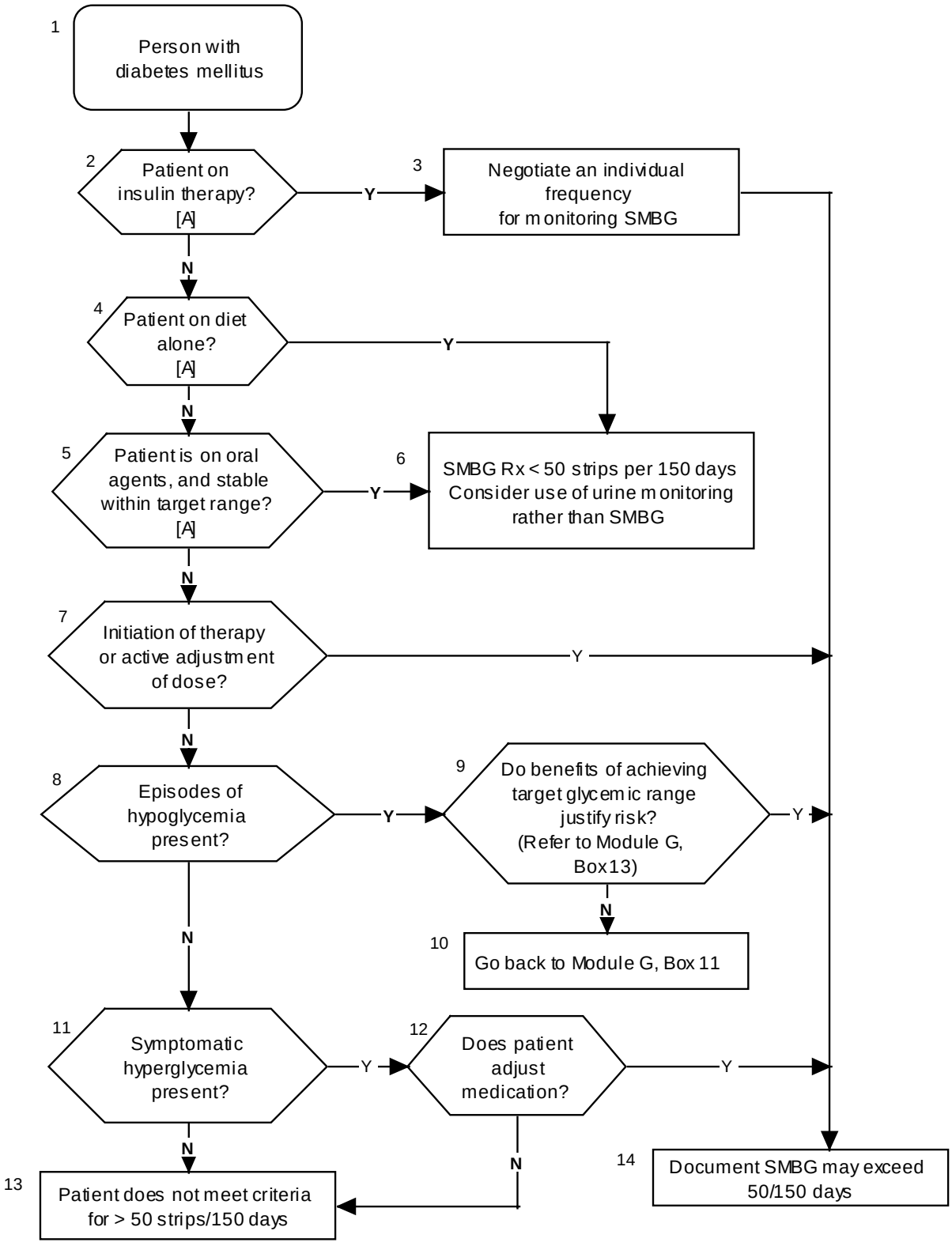
F. Follow-up

- Instruct patient to call with questions/concerns.
- Send copy of Initial Assessment and Nutrition Progress Notes to referral source and place original in patient's medical record.
- Call patient 24 to 48 hours prior to next appointment to confirm.
- Individualized initial therapy: Based upon clinical judgment and factors such as motivation, educational level, and available time. For less complicated cases 3 or 4 visits over 3 to 6 months can usually be combined with other visits for the convenience of the patient, with subsequent follow-up as appropriate.

MODULE GH

GLYCEMIC CONTROL: Home Monitoring

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control: Home Monitoring



MODULE GH

GLYCEMIC CONTROL: Home Monitoring

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control: Home Monitoring Annotations

Module GH

A. Use of Self Monitoring Blood Glucose (SMBG) in Persons with Type II Diabetes Not on Insulin

TABLE OF EVIDENCE
SELF MONITORING OF BLOOD GLUCOSE

Intervention	Reference	Strength of Recommendation	Level of Strength
SMBG	Allen et al. 1990;	IIb	B
	ADA Consensus Statement: Self monitoring of blood glucose 1994;	IIb	C
	Fonborne et al. 1989;	IIb	B
	Klein et al. 1993;	IIb	B
	Wing et al. 1990.	IIb	B

1. SMBG is widely used in persons with Type II diabetes not treated with insulin without substantial scientific evidence of efficacy. Available data, based upon controlled studies, do not demonstrate that SMBG improves long term glycemic control in persons with Type II diabetes mellitus on oral medication. In several studies urine testing was as effective as SMBG, although studies did not explicitly have patients trained to self-adjust medication. Consequently, they do not exclude the possibility that selected patients, i.e., those who are highly motivated to alter their medication, diet and exercise regimen based upon SMBG results, could benefit from monitoring.

   For all patients with diabetes, practitioners should ensure that patients demonstrate proficiency with the technique (See Module G, Annotation F) including transfer of blood from finger to strip and knowledge of quality control procedures if a meter is used. If the provider does not have experience with SMBG, the patient should be referred to a diabetes educator. In addition, providers should review SMBG results at regular visits or by telephone.

   Urine testing should be considered as an alternative means of detecting hyperglycemia in patients who are not proficient with SMBG, or are not willing to make adjustments in medication or lifestyle based upon results. Use of urine testing for this purpose presupposes that the renal threshold is normal.

Recommendations for SMBG*
From VHA Pharmacy Benefits Management-Medical Advisory Panel, The Pharmacologic Management of Non-Insulin Dependent Diabetes Mellitus

Patients on Oral Agents	• For stable NIDDM: No more than 50 strips per 150 days.[a] This would allow for twice-weekly testing. Increased numbers of strips may be needed for a limited time period for the following indications: 1) initiation of therapy and/or active adjustment of oral agents 2) prevention and detection of hypoglycemia when symptoms are suggestive, or if documented hypoglycemia unawareness 3) detection of hyperglycemia when symptoms or urine glycosuria are suggestive some patients do not require strips for adequate glucose control
Patients on Insulin Alone	• The frequency of monitoring should be individualized based on the frequency of insulin injections, hypoglycemic reactions, level of glycemic control, and patient/provider use of the data to adjust therapy • A combination of pre and postprandial tests should be performed, up to 4 times per day

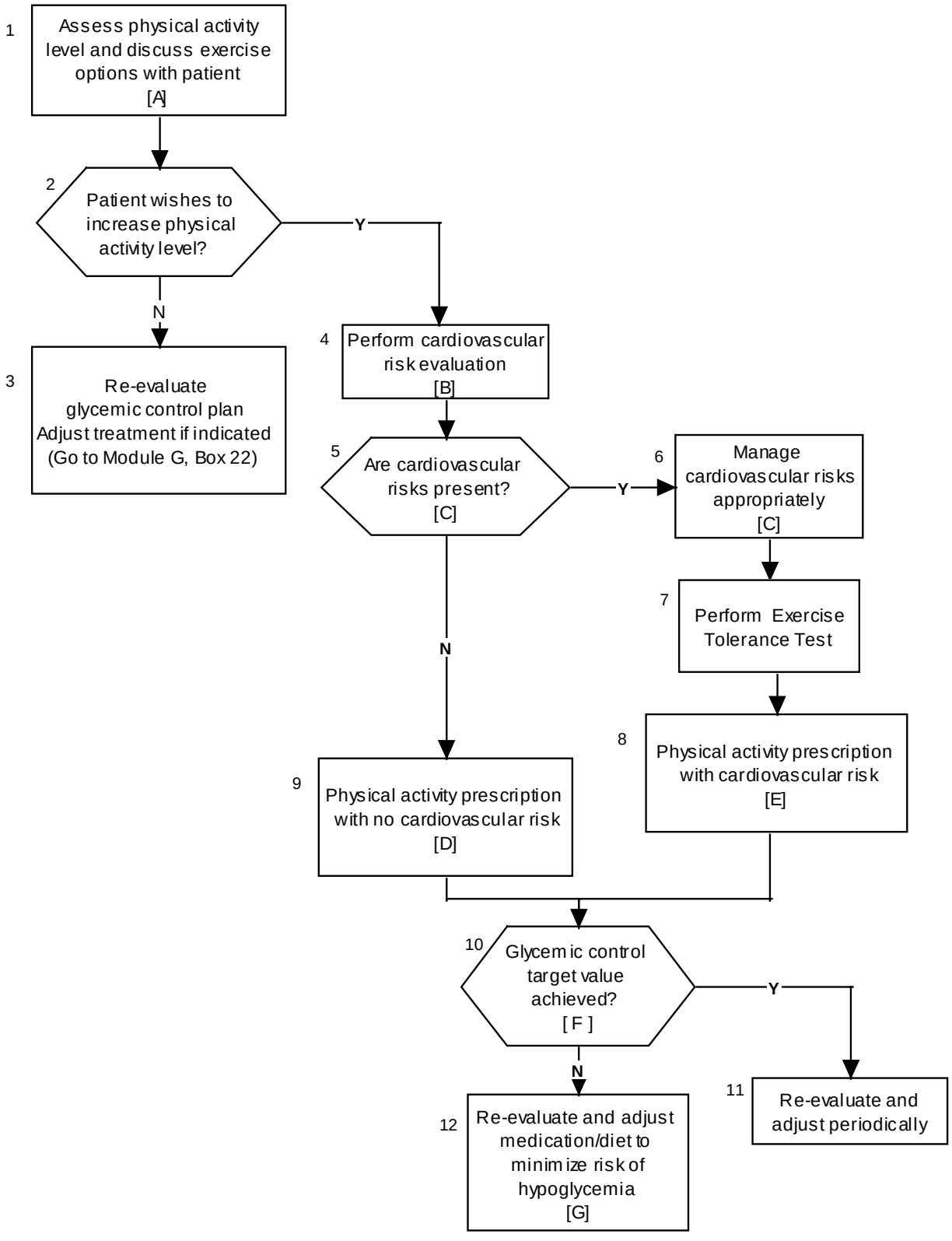
[a] SMBG should be performed only if there is a specific justification for an individual patient, and a measurable health outcome is monitored on an ongoing basis.

2. Patients who demonstrate consistent glucose results (stable patients) may require fewer or no strips. When metabolic control worsens, testing requirements may increase. Each provider must ascertain that the patient has proficiency in SMBG technique. Initial and ongoing justification for SMBG use must be provided and should be linked to health outcomes.

MODULE GP

GLYCEMIC CONTROL: Physical Activity

MANAGEMENT OF DIABETES MELLITUS
Glycemic Control: Physical Activity



MODULE GP

GLYCEMIC CONTROL: Physical Activity

ANNOTATIONS

Glycemic Control: Physical Activity Annotations

Module GP

A. Assess Physical Activity Level and Discuss Exercise Options with Patient

1. Is patient physically active or sedentary?

2. What does the patient's physical activity consist of (Walking, jogging, swimming, etc.)? How many times per week? How long?

• Less than 2 times per week	Sedentary
• 2-3 times per week	Moderately Active
• 3 or more times per week	Highly Active

Physical Activity Recommendations (General)

3. Physical activity of 10 minutes per session, several times a day can be recommended.

4. Physical activity may be incorporated in the patient's lifestyle or daily schedule. It need not be regimented.

5. An attempt must be made to increase the patient's current level of physical activity.

6. Weight training can be recommended especially for patients who cannot or do not wish to walk/jog.

7. Weight training activities should allow all major groups of muscles to work. Low weight/high repetitions should be stressed (reps: 20-30/set).

8. Activity (weight lifting) can be done several times a day, choosing a few exercises per session if patient cannot devote a lot of time at once.

9. Activities such as pushups, sit-ups, and handgrip exercises are also beneficial and should be recommended to the patient.

B. Cardiovascular Risk Evaluation — The practitioner will evaluate the patient's cardiovascular history and physical exam, including:

1. Evaluation should include a history directed towards risk or presence of peripheral vascular disease, including claudication, poor healing, amputation; cerebrovascular disease, including transient ischemic attacks and stroke; and coronary heart disease, including smoking, family history, hypertension, cholesterol (HDL to LDL ratio) and triglyceride, angina, MI, and arrhythmia.

C. Identify and Manage if Cardiovascular Risks Present — Depending upon results of the cardiovascular evaluation that is performed as part of a complete diabetes evaluation, the patient's age, and the proposed level of physical activity, it may be advisable to recommend diagnostic procedures for the presence of and/or severity of cardiovascular disease. The necessity for, and extent of, such evaluation is at the discretion of the provider. For further details one may want to refer to the Ischemic Heart Disease guideline.

D. Physical Activity Prescription With No Cardiovascular Risk

1. Ambulatory — No evidence of Cardiovascular disease.

   - 60% to 80% of *predicted maximal heart rate*
   - 3-5 times per week
   - 20-40 minutes per session
   - Aerobic type exercises

2. Non-ambulatory — No Cardiovascular disease.

   - Daily exercise with upper extremities
   - Minimum of 10 minutes per session

E. Physical Activity Prescription with Cardiovascular Risk

1. Ambulatory — Cardiovascular disease.

   - 60% to 80% of *symptom limited heart rate associated with 1.5 mm ST segment depression*
   - 3-5 times per week
   - 20-40 minutes per session
   - Aerobic exercises

2. Non-ambulatory — Cardiovascular disease.

   - Daily exercise with upper extremities

   - 60-80% of *symptom limited heart rate or heart rate associated with 1.5 mm depression of ST segment*

F. Glycemic Control Target Value Achieved? — It is evident that the risks of therapy are different for each individual, dependent upon his or her medical, social, and psychologic status. Thus, the risks of a proposed therapy must be balanced against the potential benefits. Factors for the provider and person with diabetes to consider in jointly making this decision should include the following:

1. Appropriate medical support and psychosocial environment.

2. History of severe, recurrent hypoglycemia.

3. The possible consequence of adverse effects associated with hypoglycemia (consider CVD, anticoagulation, use of dangerous equipment, etc.)

4. Alcohol or substance abuse.

5. The presence of multiple end-stage microvascular complications, including macular edema, PDR, micro- and macroproteinuria.

6. Pregnancy, or the intention to become pregnant.

7. Symptomatic cardiovascular disease.

8. Willingness and ability to self-monitor and to make appropriate lifestyle changes.

9. Quality of life.

10. Specific risks of individual therapeutic options.

G. Re-evaluate and Adjust Medication and/or Diet — To minimize risk of hypoglycemia

1. Monitor blood glucose more frequently when initiating an exercise program.

2. Decrease, *prior to exercise*, the insulin that is peaking during the exercise period. A recommended starting point is a 30% decrease for intermediate acting and a 50% decrease for fast acting insulin. However, reduction, or elimination of a dose must be individually determined.

3. Increase carbohydrate intake by 15g prior to exercise for each 30 minutes of exercise.

4. Ingest 15-30g of carbohydrate after exercise.

5. Inject insulin in an area that is not active during exercise, such as the abdomen during walking.

6. Avoid exercise during periods of peak insulin activity.

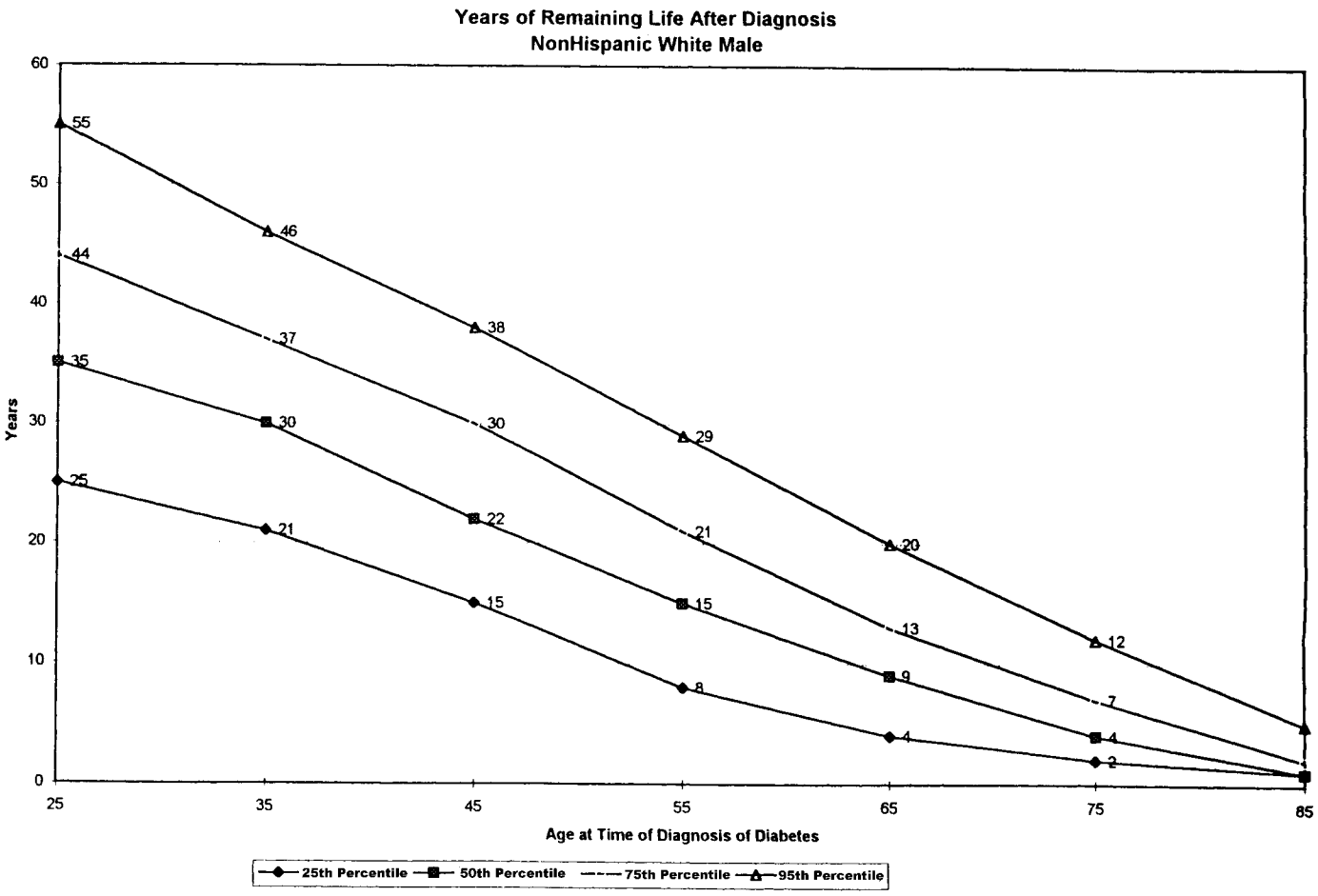
7. Exercise with a partner.

8. Monitor blood glucose after strenuous physical activity prior to bedtime.

9. Ingest a snack containing some protein, fat and carbohydrates if blood sugar <120 mg/dL.

Exhibits: G1 and G2

EXHIBIT G1


Years of Remaining Life After Diagnosis
NonHispanic White Male
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Age at Time of Diagnosis of Diabetes
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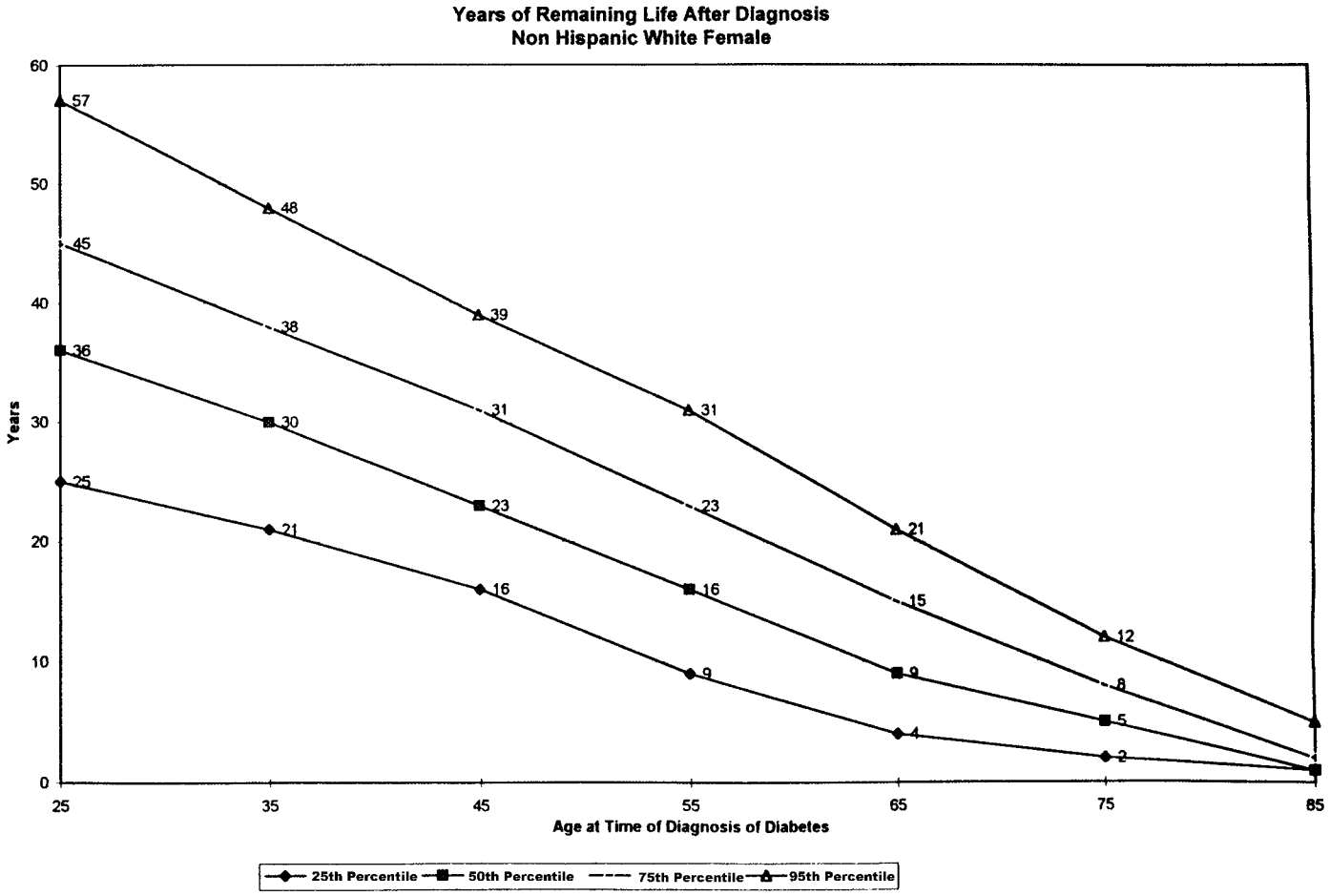
EXHIBIT G2


Years of Remaining Life After Diagnosis
Non Hispanic White Female
Years
Age at Time of Diagnosis of Diabetes
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50th Percentile
75th Percentile
95th Percentile
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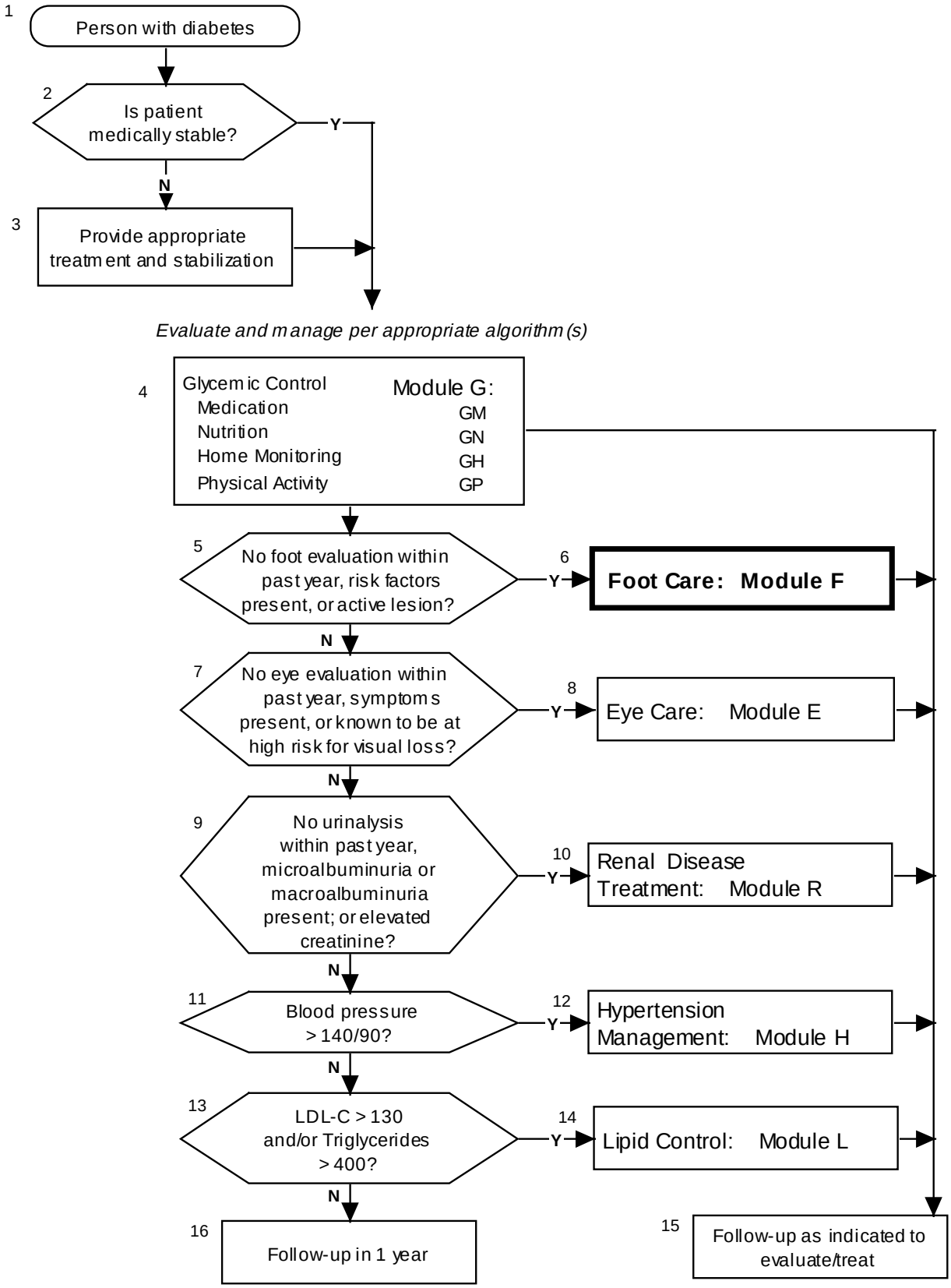
MODULE FR

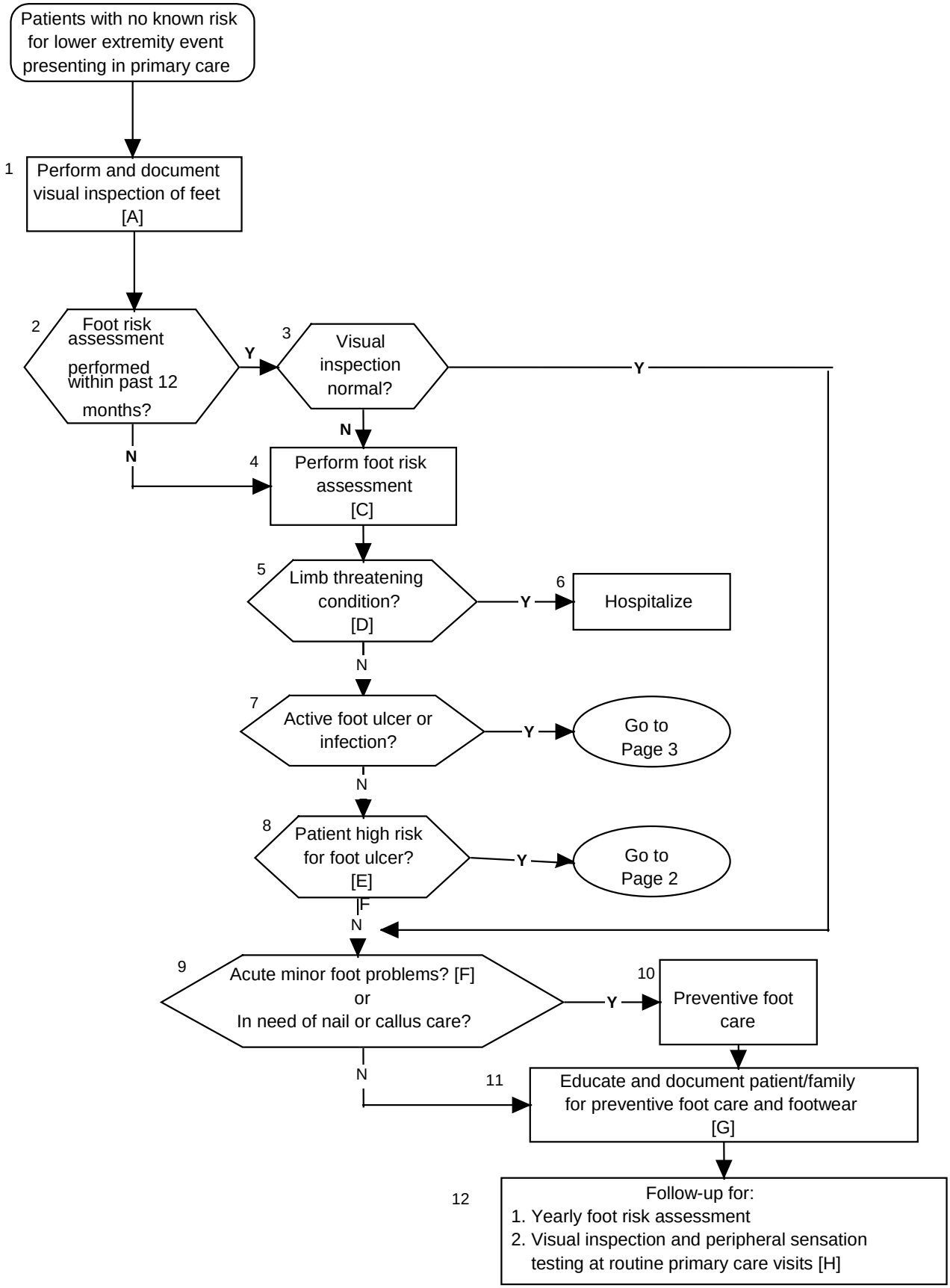
Foot Care: Routine Care

MANAGEMENT OF DIABETES MELLITUS

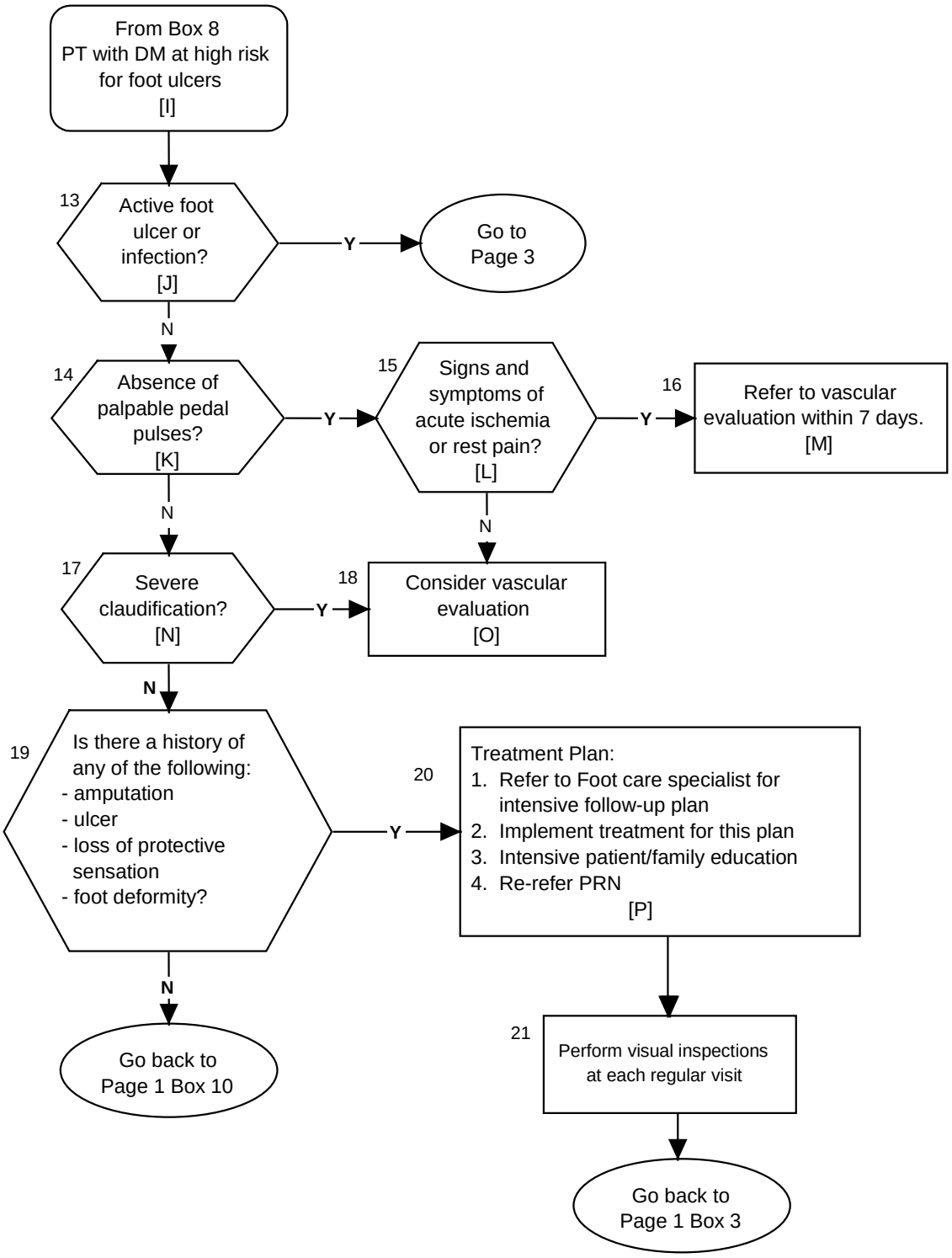


MANAGEMENT OF DIABETES MELLITUS

Foot Care: Routine Care



Foot Care: Routine Care



MODULE FR

Foot Care: Routine Care

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS

Routine Foot Care Annotations

Module: FR

A. **Perform/Document Visual Inspection of the Feet —** Inspect for breaks in skin, erythema, trauma, pallor on elevation, dependent rubor, nail deformities, extensive callus and pitting edema.

B. **Foot Risk Assessment —** Every diabetic individual needs a documented foot risk assessment within the past 12 months to determine their risk of lower extremity amputation.

C. **Perform Foot Risk Assessment —** Include evaluation of skin for breakdown, assessment of protective sensation, lower extremity arterial disease, deformities, previous history of ulcers and amputations. Assess the patient's footwear.

D. **Limb-Threatening Condition? —** Signs and symptoms of systemic infection including gas gangrene, ascending cellulitis and lymphangitis or gangrene, no palpable pulses, signs of acute ischemia including rest pain, extreme pallor, or cold extremity.

E. **Active Foot Ulcer or Infections?**

1. **Active Foot Ulcer —** A cutaneous erosion with a loss of epithelium that extends to or through the dermis and can involve deeper tissue and is characterized by an inability to self-repair in a timely and orderly manner.

2. **Active Infection —** Although infection is not always clinically apparent, common signs and symptoms include periulcer area warmth, erythema, purulent drainage, odor and involvement of bone. Pain may or may not be present. There may or may not be lymphangitis and lymphadenopathy, and the body temperature and white blood cell count may be elevated.

TABLE OF EVIDENCE
ACTIVE FOOT ULCER

Factor	Reference	Strength of Recommendation	Level of Evidence
Lower extremity foot ulcers and amputations in diabetes	Reiber et al. (1995)	I	C

TABLE OF EVIDENCE
ACTIVE INFECTION

Factor	Reference	Strength of Recommendation	Level of Evidence
Determination of infection	ADA 1990 Eckman et al. (1995) Brodsky JW et al. (1991)	IIa IIa IIa	C C C

F. Patient High Risk for Foot Ulcers? — The presence of any of the following characteristics equals high risk:

1. Lack of sensation to Semmes-Weinstein 5.07 monofilament at one or more noncallused plantar sites.

2. Evidence of lower extremity arterial disease as follows:

   a. Absence of both dorsalis pedis and tibialis posterior pulses

   b. Dependent rubor or pallor on elevation

   c. History of rest pain or claudication (pain occurring in calf or thigh when walking less than one block that is relieved by rest)

   d. Prior history of lower extremity bypass surgery

3. Foot deformities, specifically hammertoes, claw toe, Charcot's foot

4. History of foot ulcer or nonwar-related lower extremity amputation at any level

G. Acute Minor Foot Problems? — Presence of callus, onychomycosis, painful corn, or other minor problems.

H. Treat Problem As Appropriate — Many minor foot problems can be treated by the patient and/or family members, or general health care providers without referral to foot care specialists. If this approach is chosen, it is necessary that the patient and family members have received appropriate education regarding preventive foot care.

I. Documentation of Patient/Family Education for Preventive Foot Care and Footwear Measures — Outpatient education includes:

- Daily foot inspection and preventive care
- Skin, nail and callus care
- What to report and whom to call regarding any foot injury or abnormality
- Footwear

TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Reduction of lower extremity clinical abnormalities in patients with NIDDM	Litzelman DK et al. (1993)	I	A

J. Follow-up for:

1. **Yearly Foot Risk Assessment** — Every individual with diabetes must have had a documented foot risk assessment within the past 12 months to determine their risk of lower extremity amputation.

2. **Visual Inspection and Peripheral Sensation Testing at Routine Primary Care Visits —** There is limited information, yet consensus exists in the diabetes professional community that visual inspection combined with peripheral sensation testing may reveal some occult lesions in diabetics. This practice also demonstrates to the patient the importance of foot assessment.

K. Patient at High Risk for Foot Ulcer — Refer to page 2, annotation E.

TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Documented risk factors for diabetic foot ulcer	ADA 1990	IIb	C
	Bailey et al. (1985)	IIb	C
	Birk et al. (1988)	IIa	C
	Boyko et al. (1996)	IIa	B
	Holewski et al. (1988)	IIb	C
	Mayfield et al. (1996)	I	B
	Rith-Najarian et al. (1992)	I	B
	Sims DS Jr. (1988)	IIa	C

L. Absence of Palpable Pedal Pulses? — Examine to determine presence of dorsalis pedis and posterior tibial pulses.

TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Assessment of peripheral vascular disease in diabetes	Orchard & Strandess et al. (1993)	IIa	C

M. **Signs and Symptoms of Acute Ischemia or Rest Pain? —** Lower limb pain at rest, dusky/blue or purple/black color, gangrene, or cold extremity. The pain in the toes or forefoot may be relieved by dependency of the limb in the early phases. Assessment is needed for prompt vascular/surgical intervention. Acute ischemic or avascular foot will "present with" pain, pallor, pulselessness, paresthesia and/or paralysis. (See Table of Evidence at annotation L.)

N. **Refer For Vascular Evaluation Within Seven Days —** Referral by health care provider for evaluation by a member of the VA's vascular team within 7 days.

O. **Severe Claudication? —** Does patient experience pain in the thigh or calf that occurs when walking less than one block which is relieved by rest?

P. **Consider Vascular Evaluation —** If the patient's symptoms limit his or her lifestyle, a vascular specialist can determine appropriateness of surgical intervention on a patient-specific basis.

TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Justification of vascular procedures based on outcomes of vascular interventions	Conte et al. (1995) Currie et al. (1995) Wolf et al. (1993)	IIa IIa IIa	C B A

Q. **Treatment Plan**

1. **Refer to Foot Care Specialist for Intensive Follow-Up Plan —** A designated health care provider with training and interest in the management of traumatic, infectious, neoplastic, metabolic, acquired, and congenital disorders of the foot who utilizes medical, mechanical and/or surgical treatment modalities. For prior above-ankle amputees refer to amputation algorithm.

   Mechanical modalities may include footwear recommendations, and consideration of a footwear prescription will be based upon the individual structural and clinical findings. Depth shoes should be prescribed for a patient with foot deformities and peripheral neuropathy as they can accept pressure-reducing insoles and accommodate foot deformities. In-depth shoes usually have soft leather uppers paired with a crepe or Vibram outsole. Custom-molded shoes are reserved for patients with foot deformities that cannot be accommodated in a depth shoe.

   Persons with diabetes should avoid shoes with hard soles, since they do little to reduce plantar foot pressures. Running shoes have been shown to reduce plantar pressures in individuals with diabetes; however, they may not accommodate foot deformities.

TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Appropriate use of footwear in patients with diabetes	ADA 1990 Cavanagh et al. (1987) Perry et al. (1995) Young et al. (1992) Litzeman DK et al. (1997)	IIa IIa IIa IIa I	C B B B A

2. **Implement Treatment per this Plan —** It is the responsibility of the foot care specialist to implement the patient care plan decided upon. The foot care specialist may refer the patient to the primary care physician to implement and follow up on the specialist's plan.

3. **Intensive Patient and Family Education —** Begin with an assessment of the patient's current self-care practices including asking "Do you do anything special to protect your feet?"

   Patient and family foot education should include the following components and considerations:

   a. Keep it simple and appropriate for patient's educational level.

   b. Make it interactive, including demonstrations in washing, drying, and inspecting feet; nail cutting; and suitable footwear selection, including footwear for temperature extremes.

   c. Provide opportunities for the patient to state the need for what are basics of daily skin and foot care and preventive measures.

   d. Include practice time during the educational session to demonstrate and have the patient in return demonstrate safe toenail trimming.

   e. Provide repetitive examples of and messages of how care of the feet can prevent complications. Include recommendations that distinguish minor foot problems and more serious problems that require early or immediate professional treatment, together with a name and phone number for prompt assistance.

   f. Make realistic recommendations (appropriate to the patient's physical and visual capabilities) while personalizing information and highlighting key points. This may include referral to home health care.

   g. Provide written guidelines in large print and/or graphics that the patient can hang in a bathroom as a reference, and reprints of lay articles. Patients should be alerted that elevation in blood sugar may be a sign of an active

or impending infection. Use of a night-light or turning on lights when getting up at night may prevent foot injuries. Patients should be made aware of potential dangers in the home.

h. For patients with high-risk feet, twice-daily inspection in good light is recommended, looking for any redness or drainage and running the hands over the foot to detect any swelling or increased local warmth. Patients with neuropathic fingers may need to enlist help or use a mirror to inspect their feet.
Before donning footwear, inspect for torn linings, rough spots, and foreign materials, e.g., sand and stones.

Alternating between pairs of shoes during the day is recommended to alleviate repetitive local pressure. A minimum of two serviceable pairs of shoes, insoles and orthoses are needed.

Educators can utilize numerous publications on patient foot care instruction that are free of charge and have no copyright restrictions. Among them are: (1) **Take Charge of Your Diabetes: Prevent Foot Problems,** (2) **Taking Care of Your Feet,** (3) **Tips on Good Foot Care from Feet Can Last a Lifetime.** Available through the U.S. Department of Health and Human Services, CDC, and AADE.

4. **Re-refer PRN** — If patient shows little response to the implemented treatment plan, he/she should be referred to the foot care specialist again for consideration of an alternative plan.

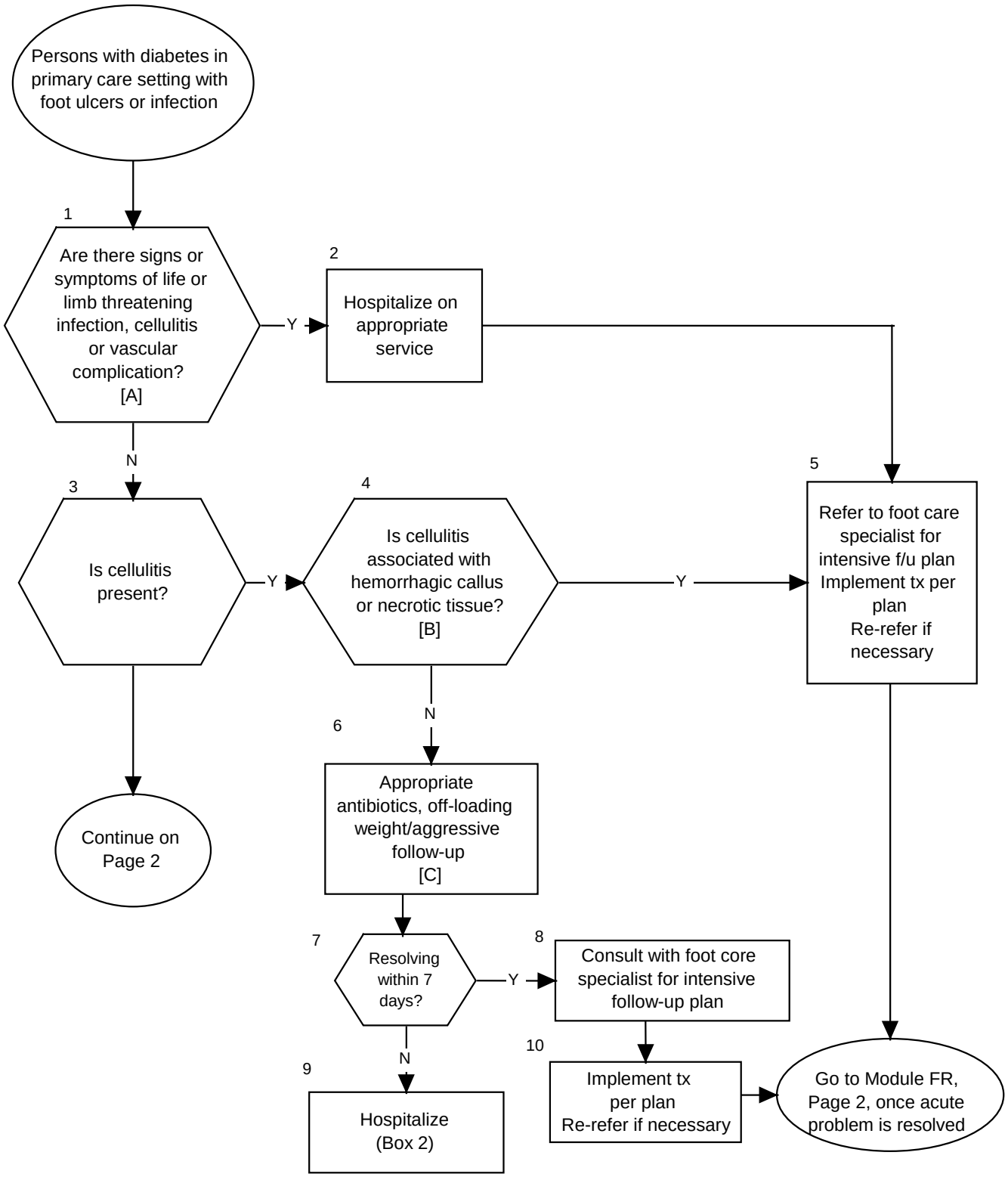
TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Patient self foot care instruction	Barth 1990	I	B
	Feste 1991	I	C
	Fain 1994	I	C
	Ahroni et al. (1993)	I	C
	Weir GC et al. (1994)	I	C

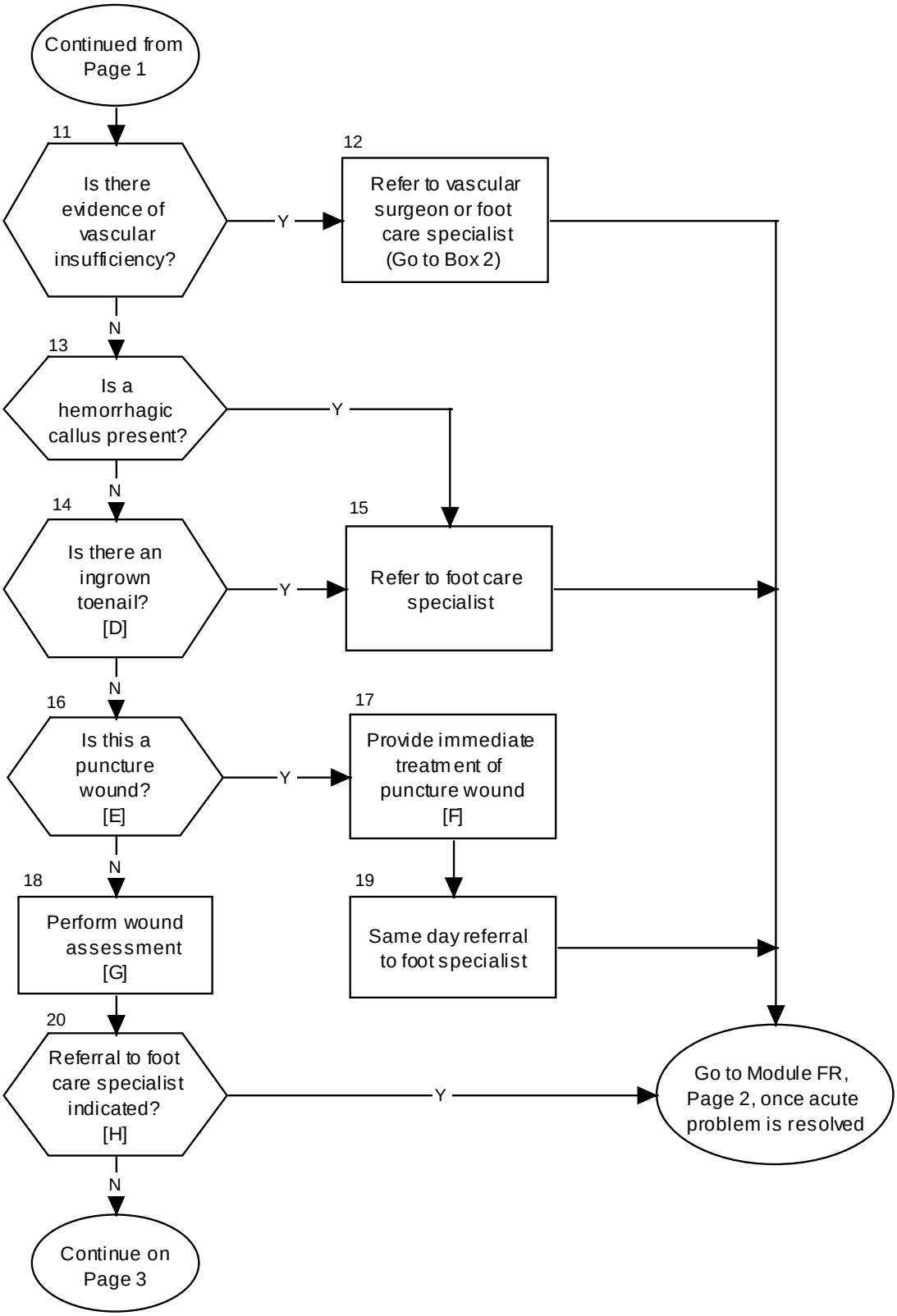
MODULE FI

Foot Care: Infection(s) and Ulcer(s)

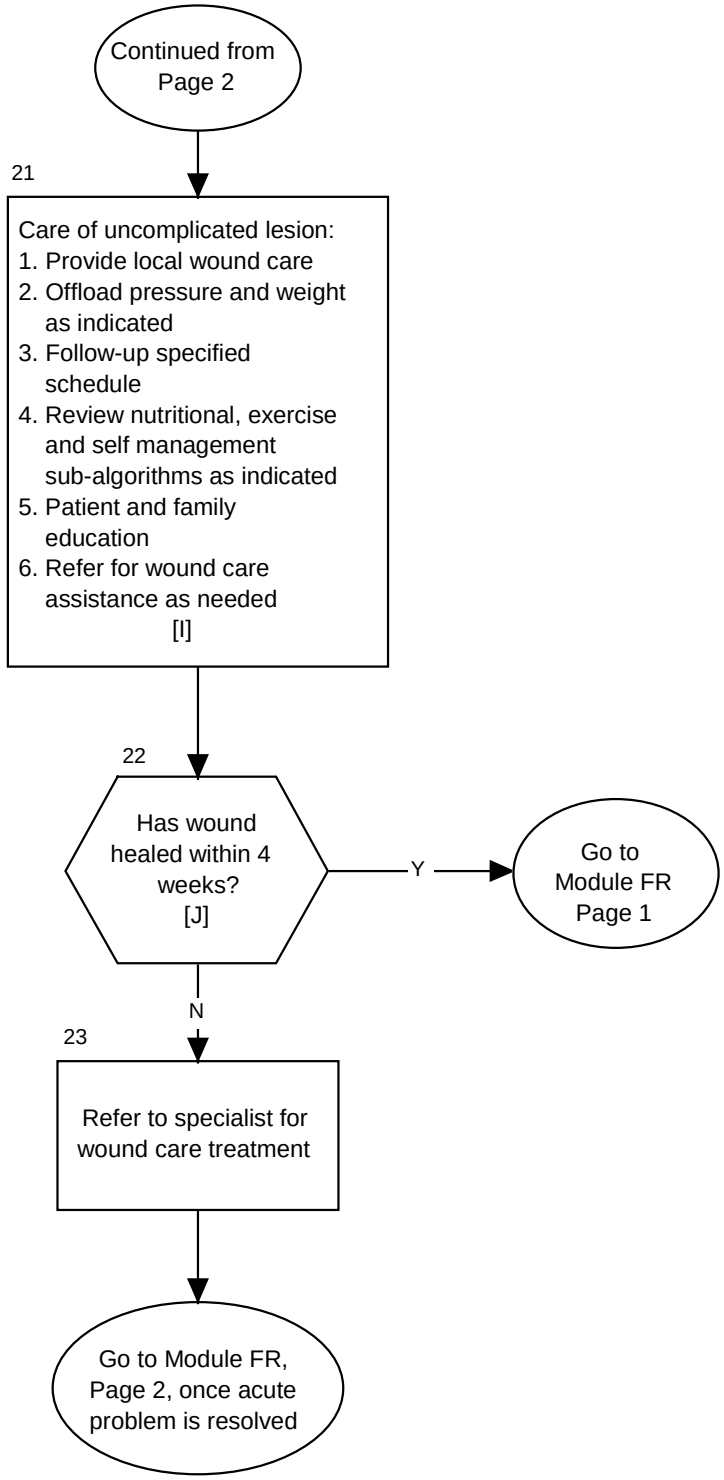
MANAGEMENT OF DIABETES MELLITUS
Foot Care: Infection(s) and Ulcer(s)



MANAGEMENT OF DIABETES MELLITUS
Foot Care: Infection(s) and Ulcer(s)



Foot Infection(s) and Ulcer(s)



MODULE FI

Foot Care: Infection(s) and Ulcers(s)

ANNOTATIONS

A. Signs or Symptoms of Life- or Limb- Threatening Infection, Cellulitis or Vascular Complications — Signs and symptoms of vascular complications include no palpable pulses and signs of acute ischemia, e.g., resting pain, extreme pallor, and cold extremities. Signs and symptoms of systemic infection include gas gangrene, ascending cellulitis, and lymphangitis or gangrene. Is there inflammation or cellular and/or connective tissue that has a margin greater than 2 cm of erythema and evidence of an ascending infection?

TABLE OF EVIDENCE

		Strength of Recommendation	Level of Evidence
Assessment of peripheral vascular disease in diabetes	Orchard & Strandness, 1993	IIa	C

B. Is Cellulitis Associated with Hemorrhagic Callus or Necrotic Tissue? — Is There nonviable tissue present that may be covering an underlying lesion or a break in the cutaneous barrier extending to or through the dermis that is not undergoing timely self-repair.

C. Appropriate Antibiotics, Off-loading Weight, Aggressive Follow-Up — See Module FR, page 1.

D. Is There An Ingrown Toenail? — Is there a nail plate that has pierced the surrounding periungual tissue with associated erythema and drainage or an area of thick or discolored callus?

E. Is this a Puncture Wound? — A lesion through the epidermis, dermis and other tissues caused by a piercing or penetrating object.

TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Treatment of puncture wounds	Lavery et al. (1995)	II	C

F. Provide Immediate Treatment of Puncture Wound — Initiate antibiotics, cleanse wound, ensure adequate tetanus coverage and same-day referral to foot specialist.

G. Perform Wound Assessment — Review anatomic, physical, and lesion characteristics, including determination of circumference, depth, and involvement of deep structures. Assess for signs of infection, including necrosis, sinus tracts, exudate, odor, presence of

fibrin, and healthy granulation tissue. Assess surrounding areas for signs of edema, cellulitis, or abscess.

TABLE OF EVIDENCE

	Reference	Strength of Recommendation	Level of Evidence
Treatment of puncture wounds	Lavery et al. (1995) ADA Diabetic Foot Care 1990	IIa IIa	C C

H. Referral to Foot Care Specialist Indicated? — Lesion is a blister, erosion, and/or minor cut that does not extend beyond subcutaneous tissue. Pulses are present, there are no signs of acute infection, and there is no severe lower limb pain and no sign of a worsening lesion. An ingrown toenail should be referred to a foot specialist for evaluation for excision.

I. Care of Uncomplicated Minor Lesion

1. Provide Local Wound Care — Cleanse wound with saline, remove necrotic and callus tissue, apply appropriate dressing and other indicated treatments.

2. Offload Pressure and Weight as Indicated — Consider lesion site, then provide pressure relief to avoid further trauma to lesion site by use of a post op shoe, off-loading or depressurization footwear based on lesion site. (Special shoes and insoles, bed rest.) See Module FR, page 1.

3. Follow-Up on a Specified Schedule — VA facility specific, but patients with active lesions need to be followed at least monthly.

4. Review Nutritional, Exercise and Self-management Subalgorithms as Indicated — Reinforce nutritional, exercise, and self-management recommendations. Avoid initiation of calorie restriction diet for weight loss in patients with foot lesions.

5. Patient and Family Education — see Module FR, page 3.

6. Refer for Foot Care Assistance as Needed for Patients Unable To Do Local Wound Care — Educate a family member on local wound care or refer the patient to a home health service.

J. Has Wound Healed Within Four Weeks? — Assess for appropriate reduction in lesion size and depth and appearance of healthy granulating tissue, with no evidence of infection.

TABLE OF EVIDENCE

Factor	Reference	Strength of Recommendation	Level of Evidence
Progress for Wound Healing	ADA 1990	IIa	C

References:

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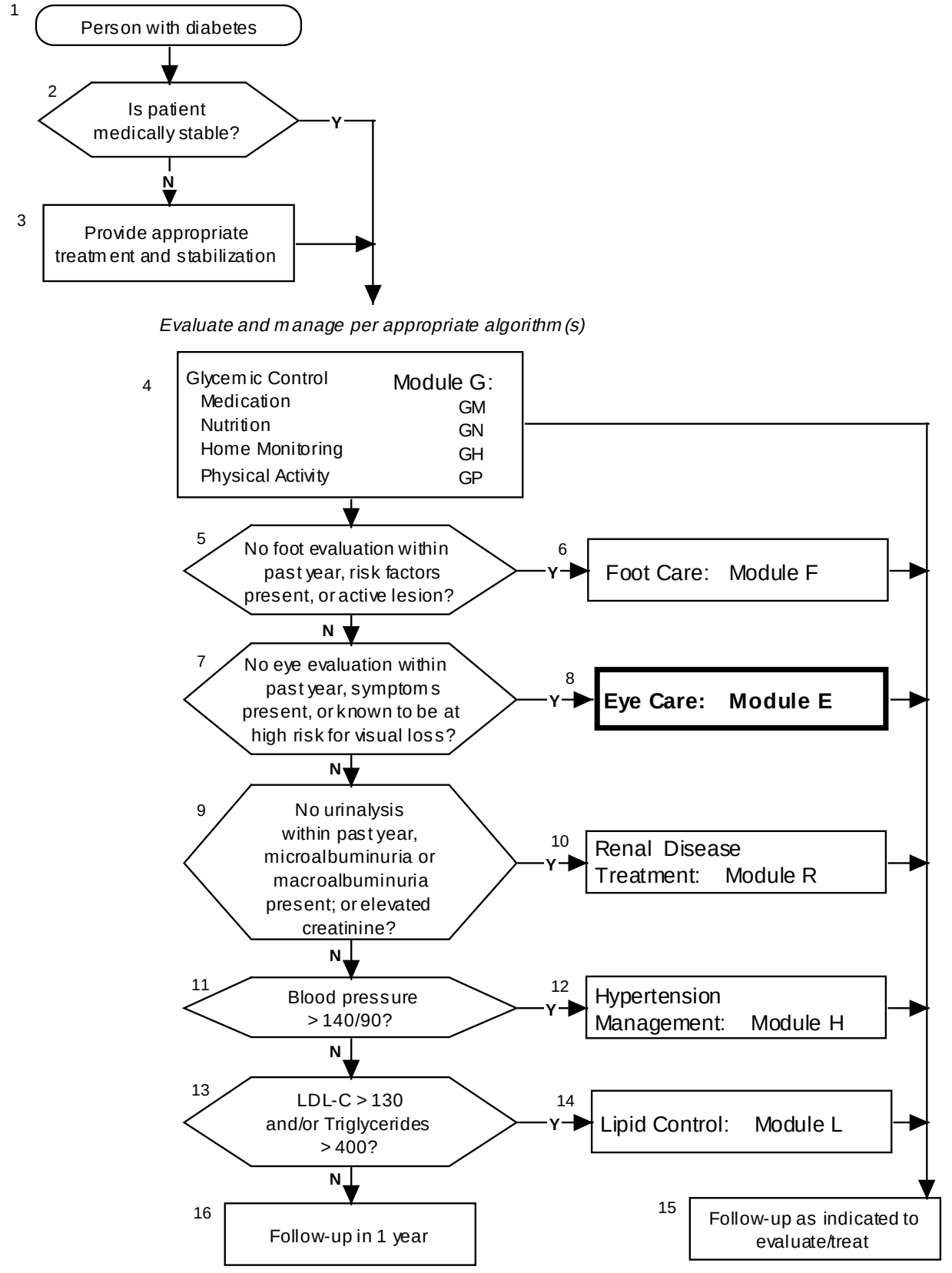
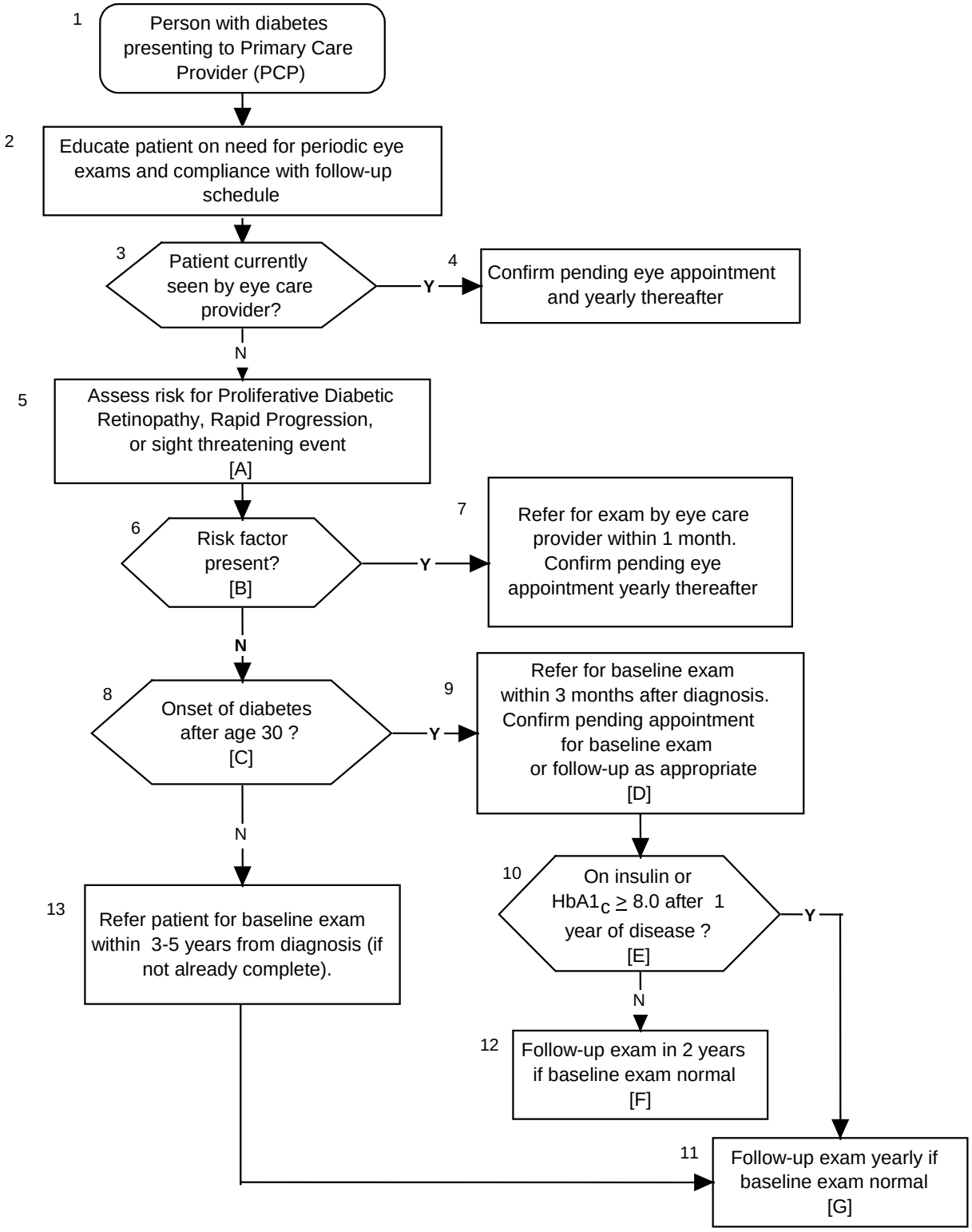
Module E:

Eye Care

MANAGEMENT OF DIABETES MELLITUS



Management of Diabetes Mellitus
Eye Care



Module E

Eye Care

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS
Eye Care Annotations

Module E

A. Proliferative Diabetic Retinopathy (PDR) — Assess risk for proliferative diabetic retinopathy, rapid progression, or sight-threatening event:

1. Presence of lower extremity amputation (diabetes related).

2. Gross proteinuria (> 200 μg/min), elevated creatinine dialysis dependent, or post transplant.

3. Duration ≥ 20 years.

4. Pregnancy.

5. Recent decrease in vision not associated with fluctuations in blood glucose.

B. Risk Factor Present?

1. Patients at high risk for proliferative diabetic retinopathy, rapid progression, or sight-threatening event should be seen on an urgent basis. Patients who have new or worsening symptoms or are pregnant should be referred for re-evaluation even if they have had an eye examination within the past year.

2. Eye exam implies a comprehensive dilated eye examination by an ophthalmologist or optometrist and includes indirect and slit lamp ophthalmoscopy.

3. The primary care provider should confirm yearly that the patient is being followed with dilated eye examinations.

4. Non-dilated retinal examinations by providers other than eye care specialists are relatively insensitive in detecting retinopathy.

5. Frequency of causes of visual impairment in other than retinopathy older onset diabetic patients dictates a comprehensive eye exam.

6. Fundus photography is appropriate and effective for retinopathy screening.

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
Dilated comprehensive exam by eye care provider	Nathan et al. (1991) Singer et al. (1992) Klein et al. (1984) Panel consensus	I I I	B C B

C. Onset of Diabetes After Age 30 — For patients diagnosed with diabetes < 30 years of age, the risk for retinopathy becomes significant after 3-5 years of the disease onset.

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
Initial eye exam after 3 to 5 years' duration for early-onset (<30) diabetes	Klein et al. (1992) Klein et al. (1989)	I I	B B

D. Refer to Baseline Exam Within 3 Months After Diagnosis — A significant minority of patients 30 years of age or older may have retinopathy at the time of diagnosis.

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
Initial eye exam within 3 months after diagnosis for older-onset (<30) diabetes	Klein et al. (1989) Klein et al. (1992)	I I	B B
Yearly eye exam for early onset patients and older-onset (≥ 30) on insulin	Javitt et al. (1990) Javitt et al. (1989) Dasbach et al. (1991)	I I I	B B B

E. On Insulin or $HbA_{1c} \geq 8.0$ After 1 Year of Disease — A yearly eye exam for older-onset patients on insulin (Type II diabetes) is cost effective in preventing vision loss.

F. Follow-Up Exam Within 2 Years if Baseline or Any Subsequent Exam Normal — An every-other-year examination is cost effect in preventing vision loss in noninsulin-requiring older-onset diabetic patients.

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
Yearly eye exam for poorly controlled noninsulin-requiring older onset patients	Klein et al. (1995)	I	B
Every-other-year eye exam for well-controlled noninsulin-requiring older-onset patients	Dasbach et al. (1991)	IIa	B

G. Follow-Up Exam Yearly if Baseline or Any Subsequent Exam Normal — Poor control in non-insulin-requiring diabetes is associated with a risk for retinopathy progression similar to that for patients on insulin.

References:

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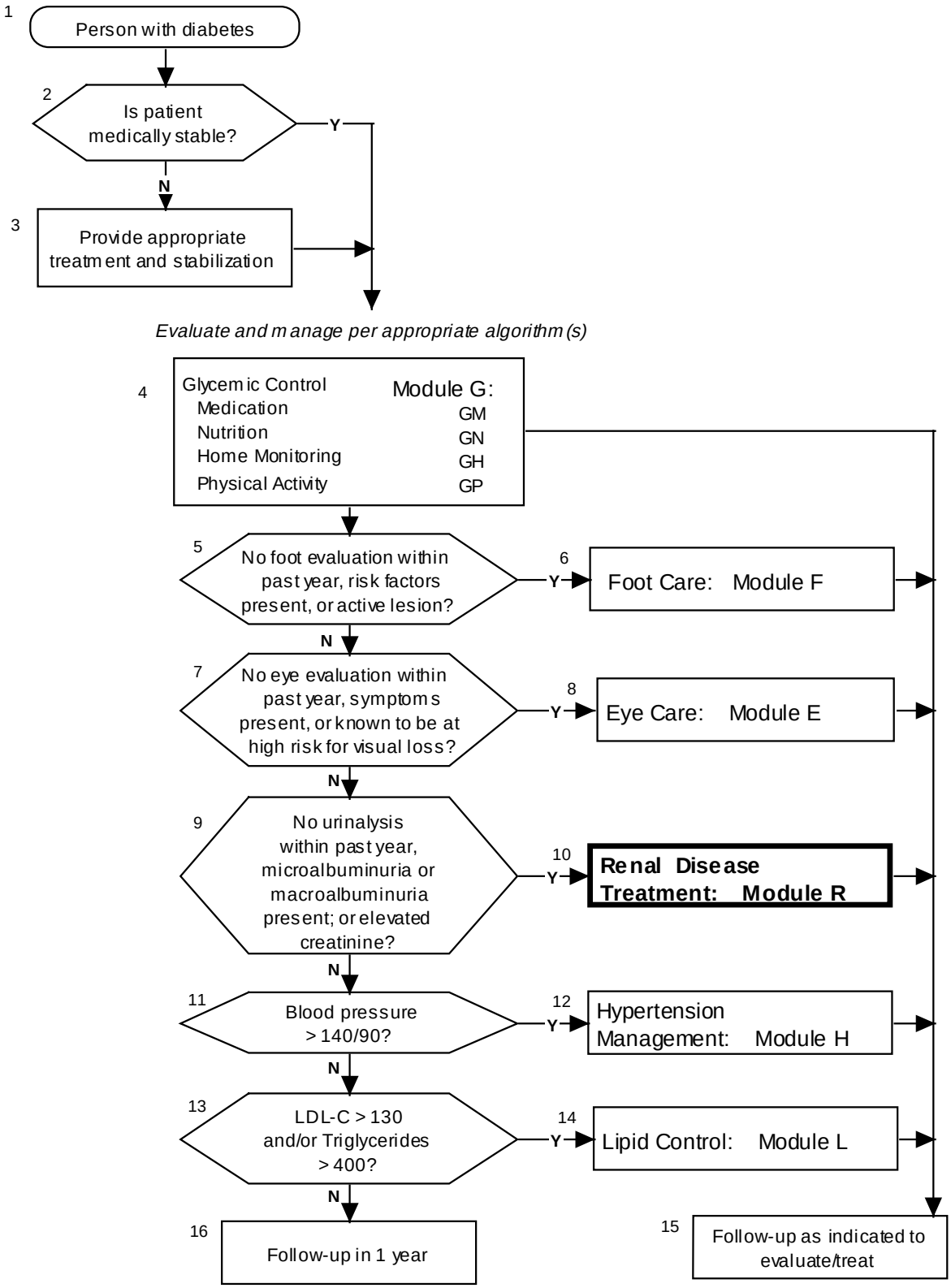
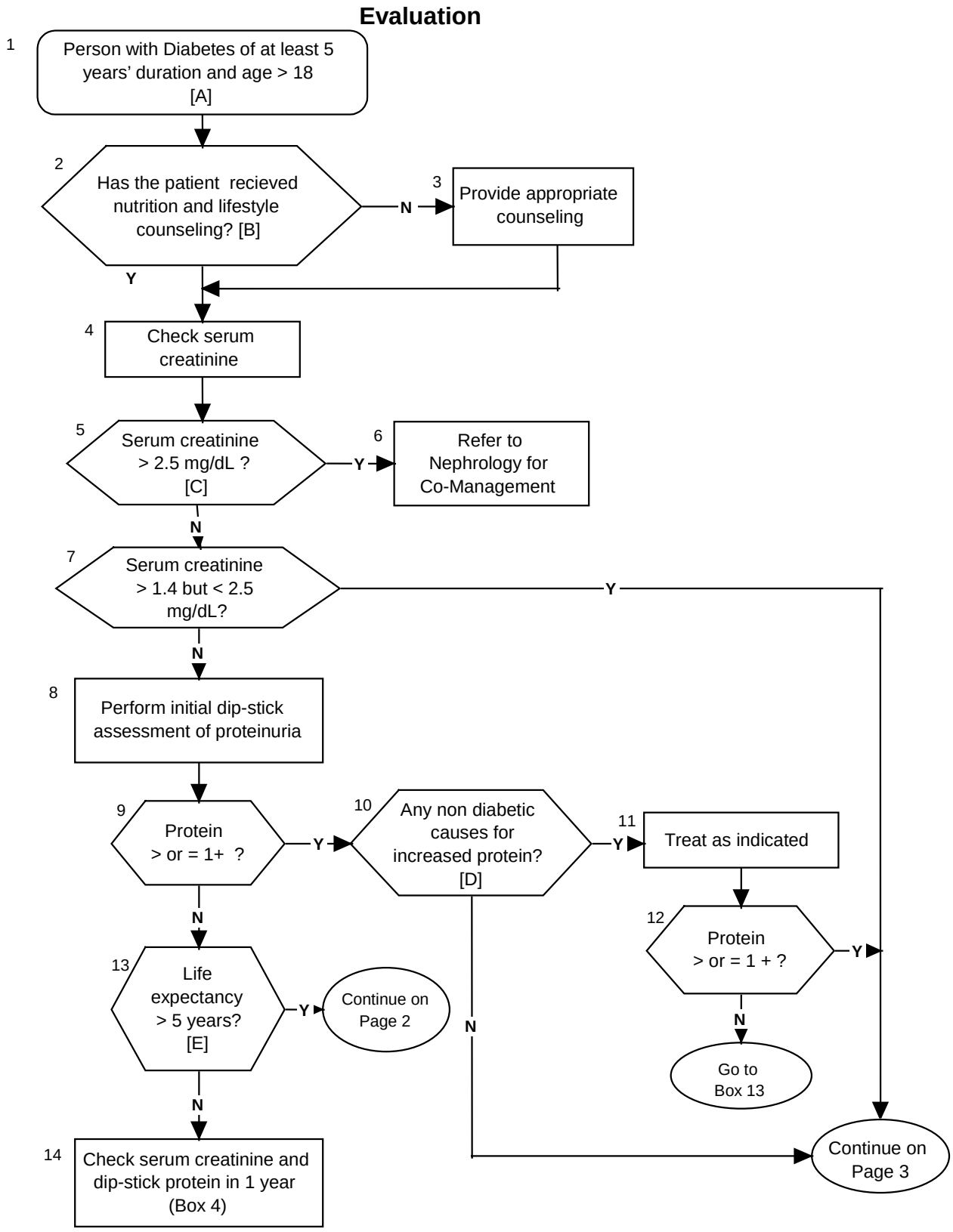
Module R:

Renal Disease Treatment

Management of Diabetes Mellitus

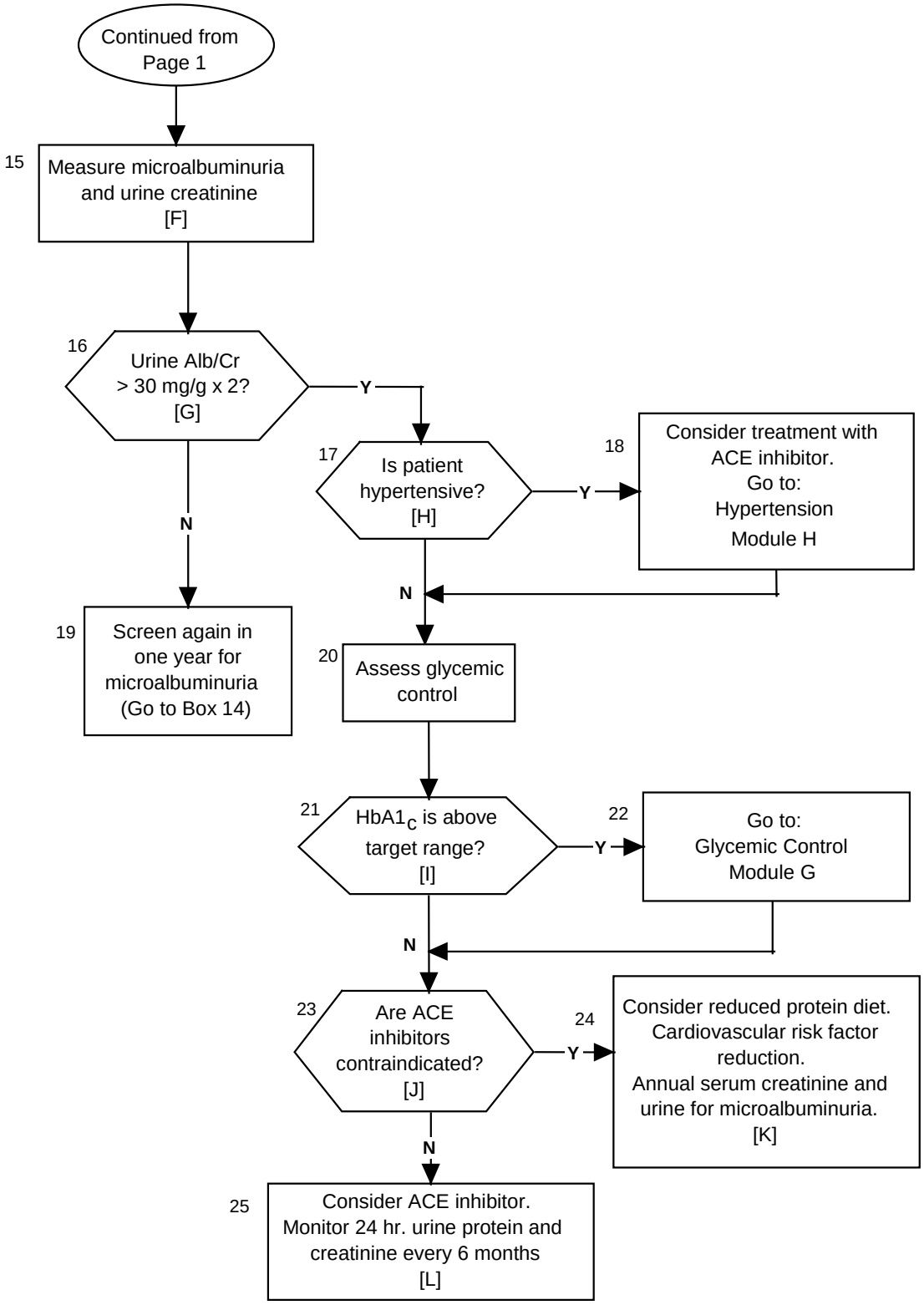


Management of Diabetes Mellitus
Renal Disease Treatment



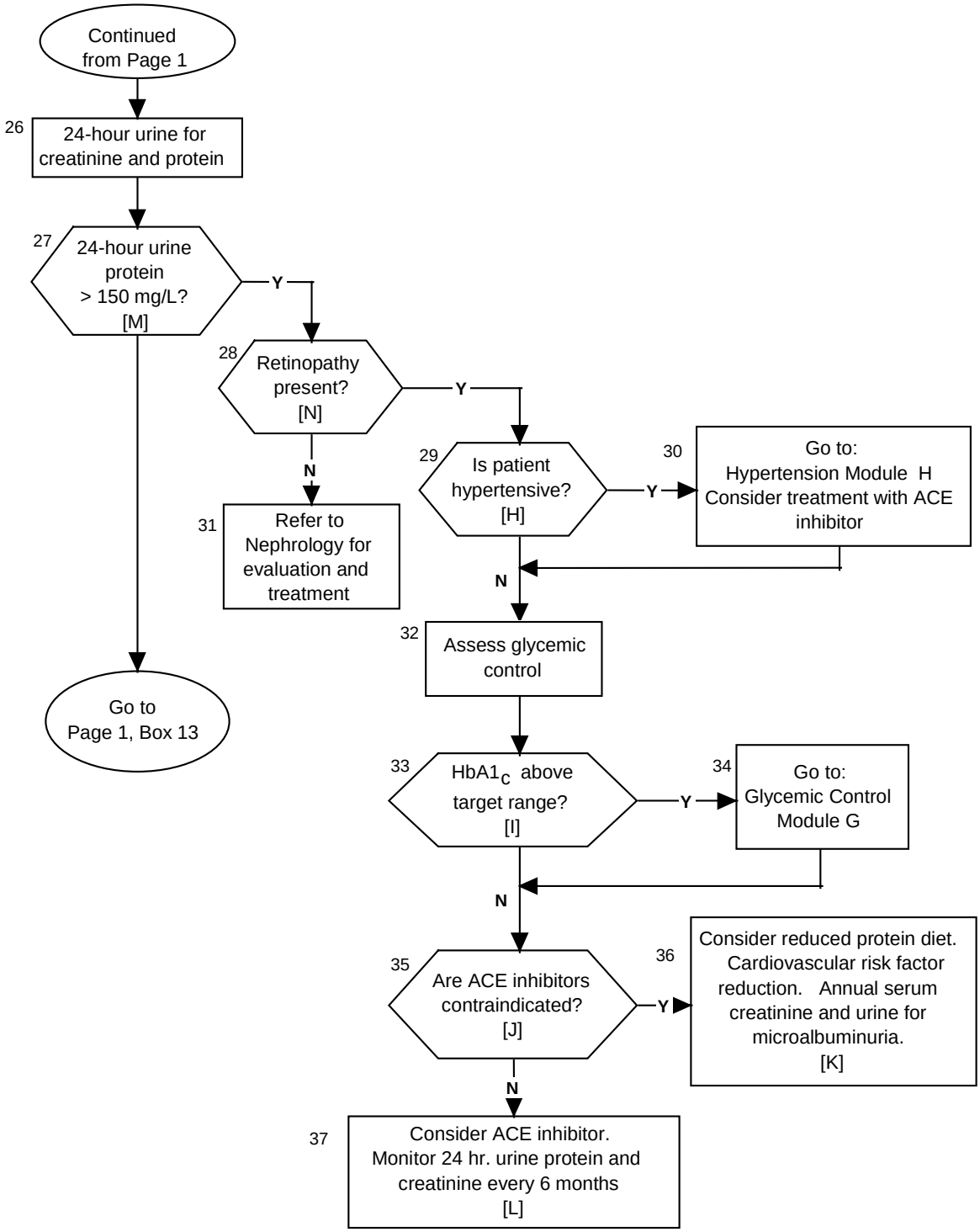
Management of Diabetes Mellitus
Renal Disease Treatment

Screening



Management of Diabetes Mellitus
Renal Disease Treatment

Management



Module R

Renal Disease Treatment

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS
Renal Disease Treatment

Module R

A. Person with Diabetes of at Least 5 Years' Duration and Age > 18—Algorithm derived primarily from National Kidney Foundation (Bennett et al. 1995); and American Diabetes Association (1994, 1995, 1997). Deviations from these recommendations are shown below:

TABLE OF EVIDENCE

Treatment and Diagnostics	Veterans Affairs	National Kidney Foundation[1]	American Diabetes Association[2]
Age limit to screening for microalbuminuria	No upper age limit, rather no screening if life expectancy < 5 years	Do not screen after age 70	No upper age limit
Urine specimen	Random with albumin/creatinine ratio, overnight timed, or 24-hour	Random with albumin/creatinine ratio	Timed urine collection or an albumin-to-creatinine ratio in a random urine specimen
Scope	Deals with elevated creatinine, proteinuria as well microalbuminuria	Starts after tests show that the serum creatinine is negative and there is no proteinuria	Both proteinuria and albuminuria
Nephrology referral	Creatinine > 2.5 or 24-hour total urinary protein >150 mg/L and absence of retinopathy	Albumin/creatinine ratio > 300 mg/g; ACE inhibitor adverse effect (creatinine increase of > 1mg/dL or serum potassium of > 5.0 mEq/L 1-week after starting ACE)	1994: GFR < 70 ml/min or when serum creatinine > 2 mg/dL or when difficulties occur in management of hypertension or hyperkalemia; 1997: When the GFR begins to decline substantially

TABLE OF EVIDENCE

#	Variables	Reference	Strength of Recommendation	Level of Evidence
1	Consider ACE inhibitor in absence of hypertension	Viberti 1994; Marre 1988; Marre 1991; Mathiesen 1991	I I I I	A A A A
2	Consider ACE inhibitor in presence of hypertension	Lewis 1993	I	A
3	Monitor every 6 months	Bennett et al. 1995	I	C
4	Screening for diabetic renal disease	Bennett et al. 1995; American Diabetes Association 1994, 1995, 1997	I I	C C

B. Has Patient Received Nutrition and Lifestyle Counseling?

1. Regular physical activity

   a. Minimum goal

      - Regular physical activity
      - Small increase over current level
      - Progression to level that achieves cardiovascular fitness (e.g., 30 minutes of brisk walking most days of the week)
      - Muscular strengthening and joint flexibility

   b. Recommendations

      (1) Essential components of a systematic, individualized exercise prescription include the appropriate mode, intensity, duration, frequency, and progression of physical activity.

      (2) Assess risk, preferably with exercise test to guide prescription.

      (3) Advise medically supervised programs for moderate- to high-risk patients.

      (4) Consider level of fitness, medications that may influence heart rate, risk of cardiovascular or orthopedic injury, individual preferences, and individual program objectives.

      (5) Encourage minimum of 30 to 60 minutes of moderate intensity activity, 3 to 4 times weekly (e.g., walking, jogging, cycling or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, using stairs, gardening, household work). Minimum benefit, 5 to 6 hours per week.

      (6) Light to moderate physical activity requires sustained, rhythmic muscular movements, is equivalent to sustained walking, performed at less than 60% of maximum heart rate for age. Maximum heart rate equals roughly 220 beats per minute minus age.

2. Smoking Cessation

   a. Goal

      - Complete cessation

b. Recommendations

(1) A cigarette smoker is defined as one who has smoked at least 100 cigarettes and who currently smokes cigarettes.

(2) Regular exposure to tobacco smoke is defined as the occurrence of tobacco smoking anywhere in the home for more than 3 days each week.

(3) A smokeless tobacco user is defined as one who has snuffed or chewed tobacco at least 20 times and who currently uses snuff or chewing tobacco.

(4) Every person who smokes should be offered smoking cessation treatment at each visit.

(5) Ask and record the tobacco use status of every patient.

(6) Cessation treatment as brief as 3 minutes is effective.

(7) The more intense the treatment, the more effective the abstinence.

(8) Nicotine replacement therapy (nicotine patches or gum), clinician-delivered social support, and skills training are effective components of smoking cessation treatment.

3. Stress Management

a. Goal

- Understand and modify stress

b. Recommendations

(1) Ways to cope with stress: Relaxation, emergency stress stoppers, exercise, reduced chemical stresses.

(2) Stress management skills: Avoid, adapt, alter, speaking up, and time management.

4. Alcohol Counseling

a. Goal

- Screening to detect problem drinking; and
- Screening to detect hazardous drinking

b. Recommendations

(1) Use of a standardized instrument (CAGE, MAST, AUDIT, etc) to screen for alcohol use is recommended. Ask patients to describe the quantity, frequency, and other characteristics of their use of wine, beer, and liquor, including frequency of intoxication and tolerance of the effect of alcohol.

(2) Suggested safe drinking — 2 drinks per day in men and 1 drink per day in women. One drink is defined as 12 ounces of beer, one 5-ounce glass of wine, or 1.5 fluid ounces (one jigger) of distilled spirits.

(3) Refer to alcohol treatment program if evidence of problem or hazardous drinking.

(4) At risk is defined by the standardized instrument or as 5 drinks per day in men, 3 drinks per day in women, frequent intoxication or intoxication resulting in hyperglycemia.

(5) Heavy drinking is defined as 5 or more drinks, once or twice each weekend.

(6) Persons who drink should be informed of the dangers of driving or other potentially dangerous activities after drinking.

(7) Use of alcohol should be discouraged in persons younger than the legal age for drinking.

5. Basic Nutrition Counseling (see also Module GN)

a. Referral to Registered Dietitian for individualized instruction in meal planning, life style modifications, and potential food/drug interactions if applicable. Referral may include those patients with:

- Newly diagnosed diabetes
- Diabetes out of control
- Diet-related complications
- Type I diabetes
- Insulin pump
- Multiple daily injections

b. Goal — Fat, cholesterol, and sodium consumption follow nutrition recommendations

- Adhere to appropriate meal pattern, exercise, and medication treatment plan to maintain blood glucose and lipids within target range and electrolytes within normal range.

- Maintain kidney function and/or slow progression of disease.

- Maintain nutrition health.

c. Recommendations — Eat a variety of foods daily:

(1) Five servings of fruits and vegetables, six servings of breads, cereals, or legumes each day, two servings each of low-fat dairy and meat products, and use fat sparingly.

(2) Calories to achieve or maintain reasonable weight (25-35 calories per kg/body weight balanced with energy expenditure).

(3) Encourage weight loss as appropriate.

(4) Limit alcohol to equal to or less than 2 drinks a day.

(5) Discuss role and effect of diet, weight loss or maintenance, physical activity, smoking cessation, and medications, hypertension, and renal disease.

d. Hyperlipidemia:

(1) Fats restricted according to risk factors and severity of serum lipid levels.

(2) Emphasize consumption of fish, poultry prepared without skin, lean meats, and low-fat dairy products.

(3) Emphasize monounsaturated fats as preferred fat (e.g., olive, canola, peanut or avocado oil).

(4) Step I: Fat < 30% total calories (10% monounsaturated fat, 10% saturated fat), < 300 mg cholesterol.

(5) Step II: Fat < 20% total calories (10% monounsaturated fat, 7% saturated fat), < 200 mg cholesterol.

(6) If triglycerides > 200 mg/dL, reevaluate whether target blood glucose goal has been achieved; limit alcohol and simple sugars.

e. Hypertension:

(1) Limit sodium consumption to < 2,300 mg/day and avoid:

(a) salt in cooking or at the table,

(b) salty or highly processed foods such as smoked, cured or highly salted meats,

(c) bouillon and standard canned soups,

(d) commercial products with high salt content,

(e) foods processed in brine, and

(f) salt seasonings and sauces.

(2) Maintain or increase foods high in potassium or if applicable, take physician-prescribed potassium supplement.

f. End-Stage Renal Disease:

Protein based on 10% of total calories:

(1) Decrease meat and dairy portions, and

(2) For a patient with diabetic nephropathy, restrict protein calories to 0.8 g/kg

g. Individualize sodium, potassium, phosphorus, and calcium:

(1) Ingest more vegetables (3-5 servings/day), and
(2) Moderate amount of fruits (2-4 servings/day) consumption

h. Vitamin/mineral supplementation as appropriate.

6. Annotations to Intensive Nutrition Counseling Referral for Nutrition Counseling — Refer to registered dietitian for individualized instruction in meal planning, life style modifications, and food/drug interactions if applicable. Referral may include those patients with:

- Newly diagnosed diabetes
- Diabetes out of control
- Diet related complications
- Type I diabetes
- Insulin pump
- Multiple daily injections

b. Goal

- Fat, cholesterol, and sodium consumption follow nutrition prescription;

- Adhere to appropriate meal pattern, exercise, and medication treatment plan to maintain:

  — Blood glucose and lipids within target range and keep electrolytes within normal range;

  — Kidney function and/or slow progression of disease; and

  — Nutrition health.

c. Recommendations

(1) Adjust goals and/or nutrition prescription.

(2) Review records and evaluate adherence and understanding of:

- percent fat intake and type of fat;
- protein intake;
- carbohydrate intake;
- soluble fiber intake;
- physical activity;
- alcohol intake; and
- tobacco consumption

(3) Provide home-management training and materials.

(4) Assess change in weight, tobacco habit, physical activity, medications, and laboratory values.

(5) Review educational materials on:

- food labeling;
- recipe modification;
- soluble fiber;
- weight reduction, if applicable;
- dining out; and
- if change in medication, potential food/drug interaction.

C. Serum Creatinine Greater than 2.5 mg/dL — Although the ADA recommends referral at 2 mg/dL, the consensus of our VA panel was that 2.5 mg/dL was more appropriate for our population. Although the ADA recommends referral, when the GFR begins to decline substantially (< 70 ml. min $^{-1}$. 1.73m $^{-2}$), difficulties in obtaining an accurate collection of a 24-hour urine precluded its recommendation as a routine test.

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
Creatinine level at which referral to nephrologist is appropriate	ADA 1994, 1997; VA Consensus Panel 1997	IIa	C

D. Any Nondiabetic Causes for Increased Protein? — "Heavy exercise, urinary tract infection, acute febrile illnesses, and heart failure may transiently increase urinary albumin excretion; thus, screening should be postponed in these situations. Similarly, drugs that may alter urinary protein excretion rate, such as nonsteroidal anti-inflammatory agents or angiotensin-converting enzyme inhibitors, should be avoided during screening." (Bennett et al. 1995; ADA 1996).

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
Conditions causing transient proteinuria	Bennett et al.1995; ADA 1996	I	C

FACTORS THAT TRANSIENTLY INTERFERE WITH URINARY SCREENING FOR ALBUMINURIA

Increases in Albuminuria	Decreases in Albuminuria
Blood in urine	ACE
Congestive heart failure	Malnutrition
Exercise	Nonsteroidal anti-inflammatory drugs
Excessive protein intake	
Fever	
Uncontrolled diabetes	
Uncontrolled hypertension	
Urinary tract infection	
Vaginal fluid contamination of specimen	

E. Life Expectancy > 5 Years — "If left untreated (persistent albuminuria of > 300 mg/dL), renal disease eventually leads to uremia and death after approximately 7 to 10 years" (Bennett et al.[4]1995). The NKF guidelines suggest stopping screening at age 70, but do not

give a justification for this cutoff point. Consequently, an age cutoff point has been replaced with a life expectancy cutoff point instead. The 1997 ADA recommendations acknowledge that the microalbuminuria is a less specific marker for development of overt diabetic nephropathy and ESRD in NIDDM, in part because of higher death rates from coronary artery disease. They do not identify an age cutoff point for screening, however. Mogensen (1987) showed that 20-25% of patients with Type II diabetes and microalbuminuria eventually go on to ESRD, compared with 80% of Type I patients, with the discrepancy primarily attributed to premature cardiovascular mortality. Type II diabetic patients with microalbuminuria who progress to renal failure, progress more rapidly (i.e., years vs. decades) than those with Type I (Gall et al.1991; Ordonez & Hiatt 1989).

To estimate the life expectancy of the person you are treating, refer to Glycemic Control, Module G, box 8, annotation G as well as to Exhibits GI and G2.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
No need to screen for microalbuminuria if life expectancy < 5 years	Bennett et al. 1995;	IIa	C
	ADA 1997;	IIa	C
	Mogensen 1987;	IIa	C
	Gall 1991;	IIa	C
	Ordonez & Hiatt 1989	IIa	C

F. Measure Microalbuminuria and Urine Creatinine — Recommend either a random urine sample for microalbuminuria and creatinine or a timed urine specimen. Strips are available to detect albuminuria as low as 20 mg/L but are not the recommended method, because they do not take into account possible errors from alterations in urine concentration. Cutoff points for the various specimen types listed below are adopted from ADA (1995).

DIAGNOSIS OF PROTEINURIA IN DIABETES MELLITUS

Category of Urine Protein Excretion	24-hour Urine Collection	Adjusted for Urine Creatinine	Timed Urine Collection
Normal albuminuria	< 30 mg/24 h	30 mg/g creatinine	< 20 mcg/min
Microalbuminuria	30-300 mg/24 h	30-300 mg/g creatinine	20-200 mcg/min
Macroalbuminuria	> 300 mg/24 h	> 300 mg/g creatinine	> 200 mcg/min

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Cutoff points for normal vs. microalbuminuria	Bennett et al. 1995;	IIa	C
vs. macroalbuminuria	ADA 1997	IIa	C

G. Urine Alb/Cr > 30 mg/g Twice — If the first specimen is > 30 mg/g, repeat. When repeated, make sure you have addressed the factors that can transiently elevate urine albumin (see table above). If the second specimen is also > 30 mg/g, the patient has microalbuminuria. If the second is < 30 mg/g, repeat again. "Multiple urinary measurements are necessary because as much as a 30-50% variability in day-to-day urine microalbumin measurements may occur" (Murray 1996).

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Need to repeat microalbuminuria testing until 2 of 3 are positive	Bennett et al. 1995; Murray 1996	I I	C C

H. Is Patient Hypertensive? — Hypertension is defined below.

CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGED 18 YEARS AND OLDER*

Category	Systolic, mm Hg	Diastolic, mm Hg
Normal+	≤ 130	≤ 85
High Normal	130-139	85-89
Hypertension++		
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	≧210	> 120

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Classification of BP in Adults	Rocella 1993	I	C

*Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic pressure fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For instance, 160/92 mm Hg should be classified as stage 2, and 180/120 mm Hg should be classified as stage 4. Isolated systolic hypertension is defined as a systolic blood pressure of 140 mm Hg or more and a diastolic blood pressure of less than 90 mm Hg and staged appropriately (e.g., 170/85 mm Hg is defined as stage 2 isolated systolic hypertension).

In addition to classifying stages of hypertension on the basis of average blood pressure levels, the clinician should specify presence or absence of target organ disease and additional risk factors. For example, a patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as having "stage 1 hypertension with target organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes)." This specificity is important for risk classification and management. Normal blood pressure with respect to cardiovascular risk is less than 120 mm Hg systolic and less than 80 mm Hg diastolic. However, unusually low readings should be evaluated for clinical significance. The stages of hypertension are based on the average of two or more readings taken at each of two or more visits after an initial screening.

I. Is Glycemic Control Above Target Range? — If the patient's HgA_{1c} is not within the target range set for this patient in the glycemic module, the patient should be re-evaluated using the Glycemic Control Module G.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Contraindications to ACE inhibitors	Physicians' Desk Reference, 1996	I	C

J. Are ACE Inhibitors Contraindicated? — Contraindications include:

Absolute: Pregnancy, presence of hyperkalemia (advanced renal insufficiency or hyporeninemic hypoaldosteronism), known allergy to ACE inhibitors.

Relative: Known bilateral renal artery stenosis, advanced renal disease.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Contraindications to ACE inhibitors	Physicians' Desk Reference, 1996	I	C

K. Consider Reduced Protein Diet — From the ADA (1997): "In people with NIDDM and overt diabetic nephropathy, restriction of dietary protein has been shown to retard the progression to renal failure. There is some evidence that this may also be true in NIDDM. Therefore, a protein intake of approximately the adult recommended dietary allowance, 0.8 grams per kilogram of body weight per day (less than 10% of calories), is recommended for individuals with evidence of macroalbuminuria. In IDDM and NIDDM patients with microalbuminuria, there is inconclusive evidence that a low-protein diet slows the progression of nephropathy."

1. Cardiovascular Risk Factor Reduction — Persons with diabetes and with microalbuminuria are at high risk of developing macrovascular disease. "At least three retrospective and three prospective studies have shown an increase in cardiovascular-related mortality in patients with Type II diabetes who have microalbuminuria. In a prospective study performed by Mattock, after a mean follow-up of only 3.4 years, 28% of the group with microalbuminuria had died, and 80% of these deaths were due to cardiovascular conditions" (Murray 1996). The ADA recommends aggressive management of cardiovascular risk factors such as dyslipidemia, smoking cessation, avoidance of a sedentary lifestyle, and blood pressure regulation (ADA 1994, 1995, 1997).

2. Annual Serum Creatinine and Microalbuminuria — The ADA (1994, 1995, 1997) and the NKF (Bennett et al. 1995) recommend this screening frequency.

L. Consider ACE Inhibitors and Monitor Urine Protein and Creatinine — Evidence for ACE inhibitors being effective in Type II diabetes: At least one long-term (5 years) randomized, placebo-controlled trial in normotensive Type II diabetes patients showed a decrease in proteinuria (Ravid 1993). However, while evidence for efficacy of ACE inhibitors in Type II diabetes in decreasing proteinuria is felt to be conclusive, their efficacy in chronic renal insufficiency remains to be determined.

1. Frequency of Monitoring After Therapy — The NKF: "After initiation of therapy with an ACE inhibitor, the efficacy of this intervention should be monitored by assessing the albumin creatinine ratio every 3 to 6 months. Because the urine albumin excretion rate would be expected to increase by approximately 10% to 30% per year, stabilization of the albumin creatinine ratio or a reduction in this ratio by up to 50% should be expected." It is also recommended to "check serum potassium and creatinine one week after initiation of therapy."

TABLE OF EVIDENCE

#	Variables	Reference	Strength of Recommendation	Level of Evidence
1	Start ACE inhibitor in absence of hypertension: primary evidence	Ravid 1993	IIa	B
2	Start ACE inhibitor in absence of hypertension: secondary evidence pertains to IDDM but likely to be applicable to NIDDM	Viberti 1994; Marre 1988; Marre 1991; Mathiesen 1991	I I I I	A A A A
3	Start ACE inhibitor with hypertension primary evidence	Lewis 1993	I	A
4	Start ACE inhibitor with hypertension (secondary evidence in IDDM)	Lewis 1993	I	A

M. 24-Hour Urine Protein > 150 mg/L — This level of total protein in the urine is considered to be macroalbuminuria.

N. Is Retinopathy Present? — If any level of retinopathy is present, proteinuria has a high probability of being secondary to diabetes.

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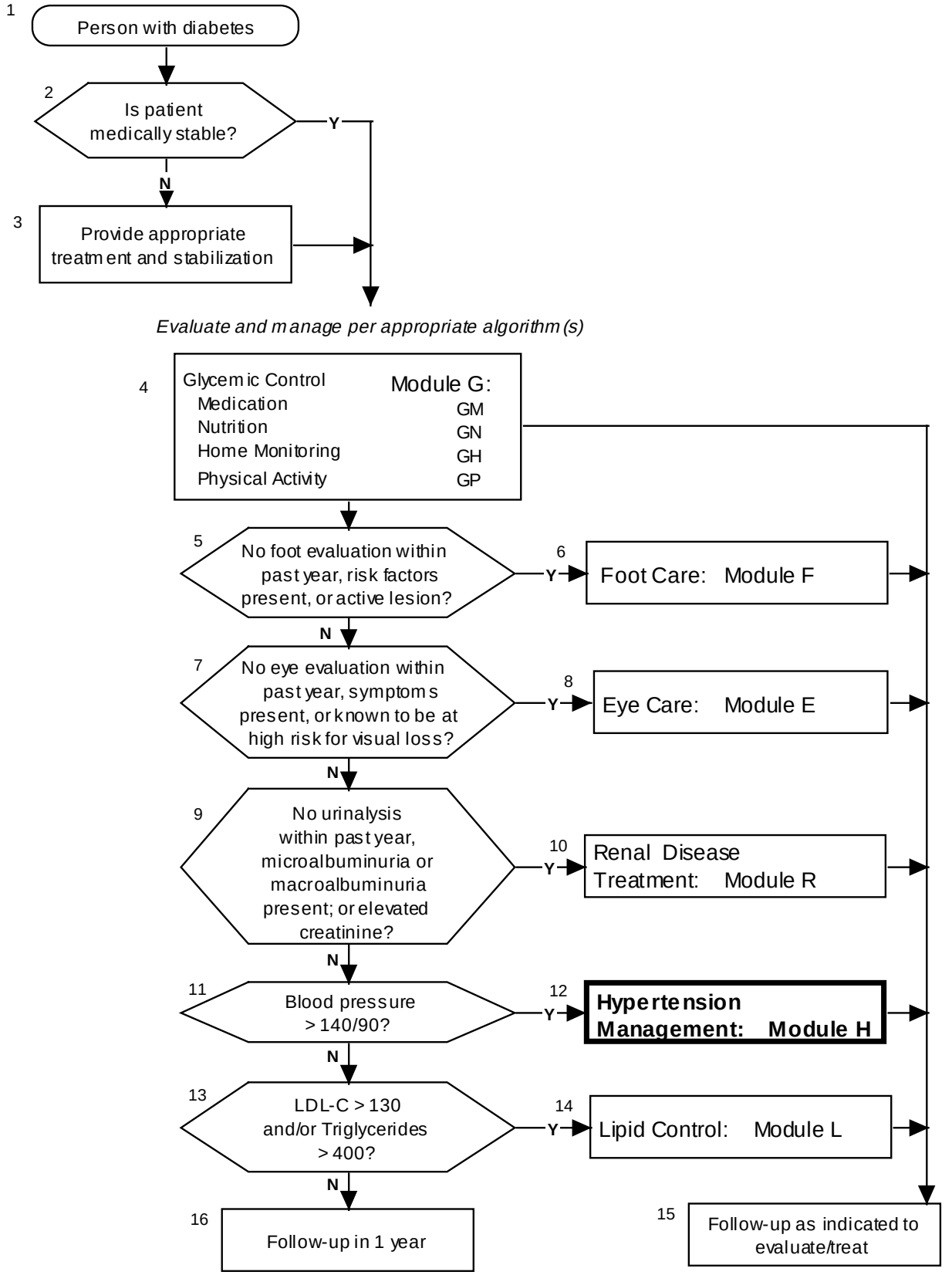
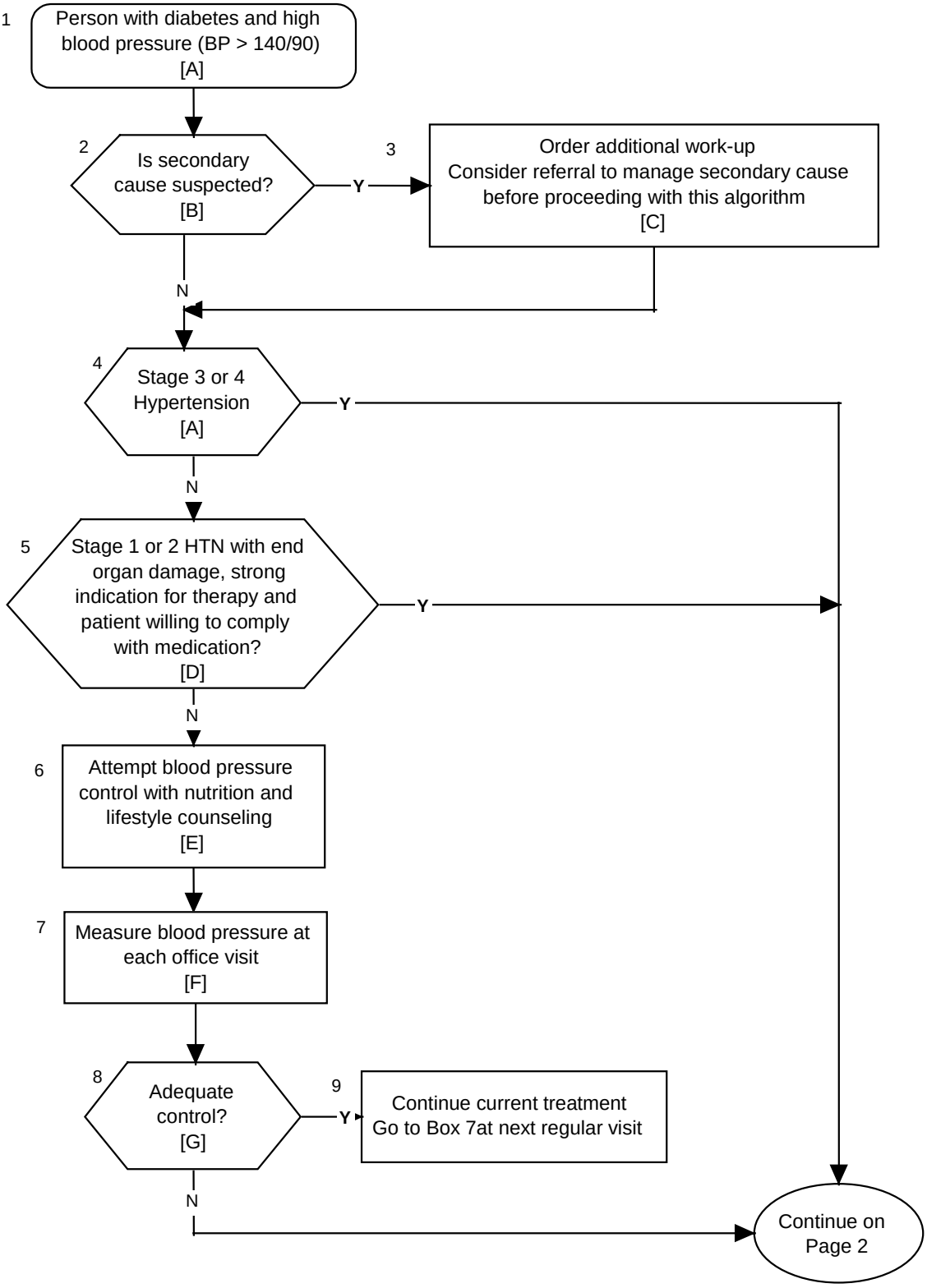
Module E:

Hypertension Management

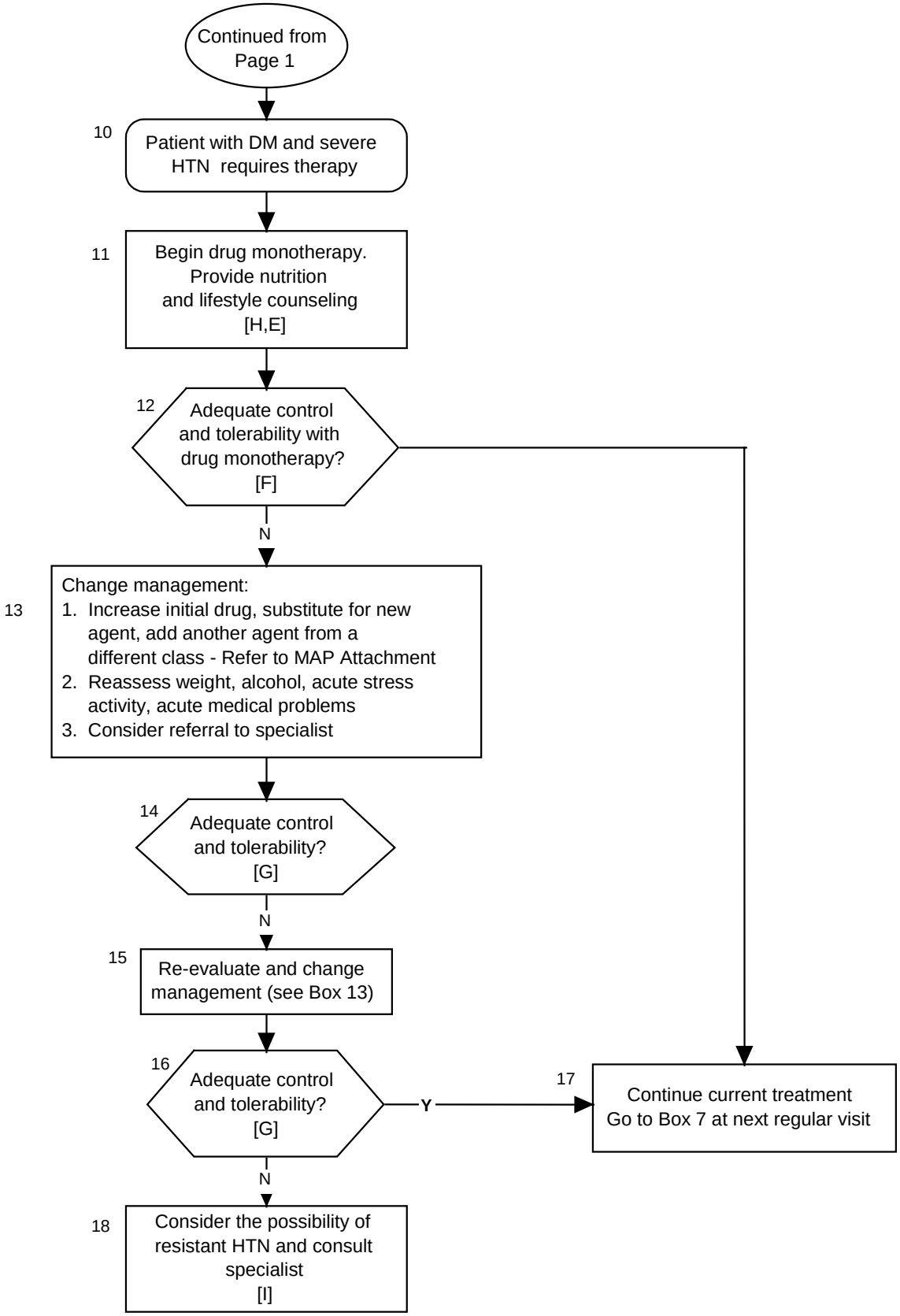
Management of Diabetes Mellitus



Management of Diabetes Mellitus
Hypertension Management



Management of Diabetes Mellitus
Hypertension Management



Module H

Hypertension Management

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS

Hypertension Management

Annotations

Module H

A. Person with Diabetes Mellitus and High Blood Pressure — Hypertension is defined by the 5th Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure and the following:

CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGED 18 YEARS AND OLDER*

	Systolic, mm/Hg	Diastolic, mm/Hg
Normal+	< 130	< 85
High Normal	130-139	85-89
Hypertension++		
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	≥ 210	≥ 120

*Not taking anti-hypertensive drugs, not acutely ill. When systolic and diastolic pressure fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For instance, 160/92 mm Hg should be classified as stage 2, and 180/120 mm Hg should be classified as stage 4. Isolated systolic hypertension is defined as a systolic blood pressure of 140 mm Hg or more and a diastolic blood pressure of less than 90 mm Hg and staged appropriately (e.g., 170/85 mm Hg is defined as stage 2 isolated systolic hypertension).

In addition to classifying stages of hypertension on the basis of average blood pressure levels, the clinician should specify presence or absence of target-organ disease and additional risk factors. For example, a patient with diabetes and a blood pressure of 142/94 mm Hg, plus left ventricular hypertrophy should be classified as having "stage 1 hypertension with target-organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes)." This specificity is important for risk classification and management. +Optimal blood pressure with respect to cardiovascular risk is less than 120 mm Hg systolic and less than 80 mm Hg diastolic. However, unusually low readings should be evaluated for clinical significance. ++Based on the average of two or more readings taken at each of two or more visits after an initial screening.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Classification of BP in Adults	Rocella 1993	I	C

B. Is Secondary Cause Suspected? — The term "secondary hypertension" implies that a patient's blood pressure elevation is a result of an underlying discoverable disease process. Secondary causes account for only a small percentage of all documented cases of hypertension, but their detection is important, as appropriate medical intervention may be curative and lead to reversal of hypertension.

Evaluate for features suggestive of rare secondary hypertension. Suspect a diagnosis of secondary hypertension in patients with abrupt onset of symptomatic hypertension, sudden loss of blood pressure control after many years of stability on drug therapy, drug resistant hypertension, and in those individuals with no family history of hypertension. Differential diagnosis of secondary hypertension includes:

- Thyroid disease (hyper- or hypo-)
- Cushing's syndrome
- Pheochromocytoma
- Primary aldosteronism
- Renovascular disease
- Renal parenchymal disease
- Aortic coarctation
- Intracerebral pathology

C. Order Additional Work-up

Early discussion or consultation with an appropriate subspecialist may lead to the most accurate and cost-effective work-up.	
Clinical Findings:	**Recommended Test/Referral:**
Features of reno-vascular hypertension: Initial onset age 50 years or older Diastolic blood pressure higher than 115 mm Hg Hemorrhages and exudates in the fundi Presence of abdominal bruit over renal arteries Diminishing blood pressure control Signs of arterial narrowing Women of child-bearing age	There is a relative contraindication to IVPs in persons with diabetes, so they are not recommended. There is no single test for reno-vascular hypertension. Consult experts in your institution. There are a variety of screening tests for reno-vascular hypertension, depending on equipment and expertise in institutions.
Features of pheochromocytoma: Paroxysms — Headaches — Palpitations — Perspiration — Pallor Extremely labile blood pressure	24-hour urine for metanephrines. Repeat with urinary catecholamines if metanephrines are normal or your suspicions are high. Consider referral to expert.
— Cushingoid features	24-hour urine for free cortisol
— Low serum potassium in absence of diuretics on two occasions	Consider primary aldosteronism and referral to Nephrology or Endocrinology
— Isolated proteinuria on two occasions	24-hour urine for protein and creatinine clearance
— Elevated serum creatinine, abnormal urine sediment, hematuria on two occasions or structural renal abnormality	Consider referral to Nephrology

[1]There are a variety of screening tests for reno-vascular hypertension, depending on equipment and expertise in institutions.

D. Stage 1 or 2 Hypertension with End Organ Damage

MANIFESTATIONS OF TARGET-ORGAN DISEASE

Organ System	Manifestations
Cardiac	Clinical, electrocardiographic, or radiologic evidence of coronary artery disease; left ventricular hypertrophy or "strain" by electrocardiography or left ventricular hypertrophy by echocardiography; left ventricular dysfunction, or cardiac failure.
Cerebrovascular	Transient ischemic attack or stroke
Peripheral vascular	Absence of one or more major pulses in extremities (except for dorsalis pedis) with or without intermittent claudication; aneurysm.
Renal	Serum creatinine $\geq$ 130 μmol/L (1.5 mg/dL);
Retinopathy	Hemorrhages or exudates, with or without papilledema

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Definitions and manifestations of target-organ disease	Rocella 1993	I	C

E. Attempt Blood Pressure Control with Nutrition and Lifestyle Counseling

1. Regular Physical Activity

   a. Minimum Goal

   - Regular physical activity
   - Small increase over current level
   - Progression to level that achieves cardiovascular fitness (e.g., 30 minutes of brisk walking most days of the week)
   - Muscular strengthening and joint flexibility

   b. Recommendations

   (1) Essential components of a systematic, individualized exercise prescription include the appropriate mode, intensity, duration, frequency, and progression of physical activity.

   (2) Assess risk, preferably with exercise test to guide prescription.

   (3) Advise medically supervised programs for moderate to high-risk patients.

(4) Consider level of fitness, medications that may influence heart rate, risk of cardiovascular or orthopedic injury, individual preferences, and individual program objectives.

(5) Encourage minimum of 30 to 60 minutes of moderate intensity activity, 3 to 4 times weekly (e.g., walking, jogging, cycling or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, using stairs, gardening, household work). Minimum benefit, 5 to 6 hours per week.

(6) Light to moderate physical activity requires sustained, rhythmic muscular movements, is equivalent to sustained walking, performed at less than 60% of maximum heart rate for age. Maximum heart rate equals roughly 220 beats per minute minus age.

2. Smoking Cessation

a. Goal — Complete cessation

b. Recommendations

(1) A cigarette smoker is defined as having smoked at least 100 cigarettes and currently smokes cigarettes.

(2) Regular exposure to tobacco smoke is defined as the occurrence of tobacco smoking anywhere in the home for more than 3 days each week.

(3) A smokeless tobacco user is defined as having snuffed or chewed tobacco at least 20 times and currently uses snuff or chewing tobacco.

(4) Every person who smokes should be offered smoking cessation treatment at each visit.

(5) Ask and record the tobacco-use status of every patient.

(6) Cessation treatment as brief as 3 minutes is effective.

(7) The more intense the treatment, the more effective the abstinence.

(8) Nicotine replacement therapy (nicotine patches or gum), clinician-delivered social support, and skills training are effective components of smoking cessation treatment.

3. Stress Management

a. Goal — Understand and modify stress

b. Recommendations

(1) Ways to cope with stress: Relax, emergency stress stoppers, exercise, reduce chemical stresses.

(2) Stress management skills: Avoid, adapt, alter, speaking up, and time management.

4. Alcohol Counseling

a. Goals

- Screen to detect problem drinking
- Screen to detect hazardous drinking

b. Recommendations

(1) Ask patients to describe the quantity, frequency, other characteristics of their use of wine, beer, and liquor, including frequency of intoxication and tolerance of the effect of alcohol.

(2) Suggested safe drinking — 2 drinks per day in men and 1 drink per day in women. One drink is defined as 12 ounces of beer, one 5-ounce glass of wine, or 1.5 fluid ounces (one jigger) of distilled spirits.

(3) Referral to alcohol treatment program if evidence of problem or hazardous drinking.

(4) At risk is defined as 5 drinks per day in men, 3 drinks per day in women, or frequent intoxication.

(5) Heavy drinking is defined as 5 or more drinks, once or twice each weekend.

(6) Persons who drink should be informed of the dangers of driving or other potentially dangerous activities after drinking.

(7) Use of alcohol should be discouraged in persons younger than the legal age for drinking.

5. Basic Nutrition Counseling

a. Referral to Registered Dietitian for individualized instruction in meal planning, life style modifications, and potential food/drug interactions if applicable. Referral may include those patients with:

- Newly diagnosed diabetes
- Diabetes out of control
- Diet related complications
- Type I diabetes
- Insulin pump
- Multiple daily injections

b. Goal — Fat, cholesterol, and sodium consumption follow nutrition recommendations:

- Adhere to appropriate meal pattern, exercise and medication treatment plan to maintain blood glucose and lipids within target range and to keep electrolytes within normal range;

- Maintain kidney function and/or slow progression of disease

- Maintain nutrition health

c. Recommendations — Eat a variety of foods daily:

(1) Five servings of fruits and vegetables; six servings of breads, cereals, or legumes each day; two servings each of low fat dairy and meat products; and use fat sparingly.

(2) Calories to achieve or maintain reasonable weight (25-35 calories per kg/body weight balanced with energy expenditure).

(3) Encourage weight loss as appropriate.

(4) Limit alcohol to equal to or less than 2 drinks a day.

(5) Discuss role and effect of diet, weight loss or maintenance, physical activity, smoking cessation, medications, hypertension, and renal disease.

d. Hyperlipidemia:

(1) Fats restricted according to risk factors and severity of serum lipid levels.

(2) Emphasize consumption of fish, poultry prepared without skin, lean meats, and low-fat dairy products.

(3) Emphasize monounsaturated fats as preferred fat (e.g., olive, canola, peanut or, avocado oil).

(4) Step I: Fat < 30% total calories (10% monounsaturated fat, 10% saturated fat), < 300 mg cholesterol.

(5) Step II: Fat < 20% total calories (10% monounsaturated fat, 7% saturated fat), < 200 mg cholesterol.

(6) If triglycerides < 200 mg/dL, ensure blood glucose is under control; limit alcohol and simple sugars.

e. Hypertension:

(1) Limit Sodium intake to < 2,300 mg/day and avoid the following:

- Salt in cooking or at the table
- Salty or highly processed foods such as smoked, cured or highly salted meats
- Bouillon and regular canned soups
- Commercial products with high salt content
- Foods processed in brine
- Salt seasonings and sauces

(2) Maintain or increase foods high in potassium, or if applicable per medication.

f. End Stage Renal Disease:

(1) Protein intake based on 10% of total calories:

- Decrease meat and dairy portions
- Diabetic nephropathy, restrict to 0.8 g/kg

(2) Individualize sodium, potassium, phosphorus, and calcium:

- Recommend more vegetables (3-5 servings/day) ingestion
- Recommend moderate amounts of fruits (2-4 serving/day) consumption

(3) Vitamin/mineral supplement as recommended by healthcare provider

6. Intensive Nutrition Counseling, Referral for Nutrition Counseling — Referral to Registered Dietitian for individualized instruction in meal planning, lifestyle modifications, and food/drug interactions if applicable. Referral may include those patients with newly diagnosed diabetes such as:

- Diabetes out of control
- Diet related complications
- Type I diabetes
- Insulin pump
- Multiple daily injections

a. Goal

- Fat, cholesterol, and sodium consumed follow nutrition prescription

- Adhere to appropriate meal pattern, exercise, and medication treatment plan to:

  — Maintain blood glucose and lipids within target range and keep electrolytes within normal range
  — Maintain kidney function and/or slow progression of disease
  — Maintain nutrition health

b. Recommendations

(1) Adjust goals and/or nutrition prescription.
(2) Review records and evaluate adherence and understanding of:

- Percent fat intake and type of fat
- Protein intake
- Carbohydrate intake
- Soluble fiber intake
- Physical activity
- Alcohol intake
- Tobacco consumption

(3) Provide self-management training and materials

(4) Assess change in weight, tobacco habit, physical activity, medications, and laboratory values.

(5) Review education materials on:

- Food labeling
- Recipe modification
- Soluble fiber
- Weight reduction, if applicable
- Dining out

- If changes in medication, potential food/drug interaction

F. Measure Blood Pressure at Each Office Visit — Measure blood pressure at each office visit, with goal to maintain BP $\leq$ 140/90. There is evidence that suggests achieving BP < 130/85 may offer increased benefit, monitoring for and avoiding symptoms of orthostatic hypertension, CHF, angina, or significantly worsened renal function.

TABLE OF EVIDENCE

	Reference	Strength of Recommendation	Level of Evidence
Continuing care	Rocella 1993	I	C

G. Adequate Control and Tolerability? — Maintain blood pressure ≤ 140/90. There is evidence suggesting that achieving a blood pressure < 130/85 may offer increased benefits. The practitioner should monitor for and avoid symptoms of orthostatic hypotension, CHF, angina, or significantly worsened renal function (National High Blood Pressure Education Program Working Group Report on Hypertension in Diabetes, 1994). VHA, Pharmacy Benefits Management—Medical Advisory Panel, The Pharmacologic Management of Hypertension is in the attachment at end of this chapter.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Definition of adequate control and tolerability	Rocella 1993	I	C

H. Begin Drug Monotherapy — See the VA Medical Advisory Panel attachment, Pharmacologic Management of Hypertension, pp 14-22, at the end of this chapter; as well as the National High Blood Pressure Education Program recommendations below:

1. National High Blood Pressure Education Program:

   a. ACE inhibitors, alpha-receptor blockers, calcium antagonists, and diuretics in low doses are preferred because of fewer adverse effects on glucose homeostasis, lipid profiles, and renal function.

   b. Beta-blockers can have adverse effects on peripheral blood flow, prolongation of hypoglycemia, and masking of hypoglycemic symptoms.

c. If proteinuria or renal disease is present (go to Module R), consider ACE inhibitor as first choice for hypertension.

d. If coronary artery disease is present, beta-blocker therapy should be considered. Also see Annotation E for nutritional and lifestyle counseling.

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
ßBlocker/CAD	Campeau et al.	I	A

2. If renal disease, consider ACE inhibitor (see table of evidence below)

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
ACE inhibitors and renal disease	Refer to renal algorithm	I	C

TABLE OF EVIDENCE

Intervention	Reference	Strength of Recommendation	Level of Evidence
Nutrition counseling	Refer to renal algorithm	I	C

I. Consider the Possibility of Resistant Hypertension — Definition of resistant hypertension: Pretreatment BP < 180/115 - failure to achieve normotension (140/90) on at least 3 different agents, including a diuretic plus 2 other classes of drugs (ß-blocker, vasodilator, Calcium antagonist, or ACE inhibitor).

- Pretreatment BP > 180/115 — failure to achieve < 160/100 on above.
- Older patients with isolated systolic hypertension — failure to reduce systolic BP to < 170 if pretreatment was > 200 or > 160 if pretreatment 160-200.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Definition of Resistant Hypertension	Rocella 1993	I	C

References

1. American College of Sports Medicine. **ACM's Guidelines for Exercise Testing and Prescription, 5th Ed.** Baltimore, Md: Williams & Wilkins, 1995.

2. American Heart Association. **An Active Partnership for the Health of Your Heart.** American Heart Association Dallas, TX, 1990.

3. Campeau L, Knatterud GL, Domansk M, Hunninghake DB, White CW, Geller NL, Rosenbeg Y. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *New Eng J Med* 1997; 336:153-165.

4. Guide to Clinical Preventive Services. 2nd Ed. Baltimore, MD: Williams & Wilkins; 1996. US Preventive Services Task Force.

5. Healthy People 2000, National Health Promotion and Disease Prevention Objectives. Washington, DC: US Department of Health & Human Services, 1991. DHHS (PHS) publication 91-50212.

6. National High Blood Pressure Education Program Working Group. Report on Hypertension in Diabetes. *Hypertension* 1994; 23(2):152.

7. Pharmacy Benefits Management—Medical Advisory Panel. The Pharmacologic Management of Hypertension. VHA PBM-SHG Publication No. 96-0003. Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs. December 1996.

8. Rocella EJ. The Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC V). *Arch Int Med* 1993; 153:161-162, 164-174.

Appendix 1. Diuretics[a-c]

THIAZIDES	DOSE[d]	COMMENTS/CAUTIONS
Hydrochlorothiazide (HCTZ)	12.5 - 25 mg/day max = 25 mg/day	• Monitor serum K^+ 2-4 wks after initiating therapy or changing dose, then q 6-12 months • Hypokalemia may potentiate digitalis toxicity • Monitor for hypotension, especially in the elderly • Thiazides may have diminished effects in patients with Cr Cl < 40-50 mL/min (or S_{cr} > 2.5 mg/dL) • Use diuretics cautiously in poorly controlled DM, symptomatic BPH, or in patients with increased risk of volume depletion • K^+-sparing combination may be preferred at higher thiazide doses • Use HCTZ/triamterene with caution with ACEI and other K^+ retaining drugs or supplement
Chlorothiazide	500-1000 mg/day max = 2000 mg/day	
Chlorthalidone	25-50 mg/day max = 50 mg/day	
HCTZ /Triamterene	initial/maintenance = 25/37.5 - 50/75 mg/day	

THIAZIDE-RELATED	DOSE[d]	COMMENTS/CAUTIONS
Indapamide	initial = 1.25 mg/day maintenance = 2.5 mg/day max = 5.0 mg/day	• Not routinely used for HTN • Reserve indapamide for patients with CrCl < 25 mL/min • Reserve metolazone for intermittent use as an adjunct for diuresis in patients with CHF or for patients with CrCl < 25 mL/min
Metolazone[e] Mykrox® Zaroxolyn®	 0.5-1 mg/day 2.5-5 mg/day	

LOOP DIURETICS	DOSE[d]	COMMENTS/CAUTIONS
Furosemide	20-80 mg/day (usually given in divided doses for HTN)	• Not routinely used for HTN • Loops may be more effective in patients with Cr Cl < 40-50 mL/min (or S_{cr} > 2.5 mg/dL) • Monitor for hypokalemia and hypotension • Higher furosemide doses may be needed for patients with nephrotic syndrome
Bumetanide	0.5-5 mg/day (usually given in divided doses for HTN)	
Torsemide	initial = 5 mg/day max = 10 mg/day	

[a] Adapted from Diuretics. In: Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1993:138a-139.
[b] Semla TP, Beizer JL, Higbee MD, eds. APhA Geriatric Dosage Handbook. 2nd ed. Hudson: Lexi-Comp Inc.,1995-96.
[c] ACEI= angiotensin converting enzyme inhibitor; CHF= congestive heart failure
[d] Once daily dosing unless specified otherwise
[e] The brand names of metolazone are not bioequivalent, therefore doses vary

Appendix 2. β-Blockers[a,b]

β-BLOCKERS	DOSE[c]	COMMENTS/CAUTIONS
Non-cardioselective[d]		• As doses increase, cardioselectivity decreases • Monitor for bradycardia, CHF, fatigue, insomnia, cold extremities, impotence, and nightmares • Monitor pulse rate • May mask the symptoms of hypoglycemia in DM • Discontinue with slow taper for 1 week • Labetalol and carvedilol may cause postural hypotension, therefore standing SBP should be monitored • Labetalol may be used in treatment of cyclosporine induced HTN • Labetalol is often used for severe HTN, and higher doses than stated may be needed in certain cases • Carvedilol dose titrations should not occur sooner than 7-14 days of initiation • Doses of carvedilol should be given with food to reduce the incidence of orthostatic effects • Agents such as acebutolol and labetalol offer fewer advantages over others, but may be necessary in restricted circumstances
Propranolol IR	80-240 mg/day (in divided doses)	
Propranolol SR	80-160 mg/day	
Cardioselective		
Atenolol	25-100 mg/day (dose adjustments are needed in CRI)	
Metoprolol	50-200 mg/day (in divided doses)	
Acebutolol	initial = 400 mg/day (once daily or divided doses) 400-1200 mg/day (in divided doses) elderly: avoid doses > 800 mg/d If CrCl< 50 mL/min, ↓ dose 50% If CrCl < 25 mL/min, ↓ dose 75%	
α & β blocking agents		
Labetalol	200-400 mg/day (in 2 divided doses)	
Carvedilol	initial = 6.25 mg/day (in 2 divided doses) max = 25 mg/day (in 2 divided doses)	

[a] Adapted from Beta-adrenergic blocking agents. In: Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1993: 157b-159m.
[b] Semla TP, Beizer JL, Higbee MD, eds. APhA Geriatric Dosage Handbook. 2nd ed. Hudson: Lexi-Comp Inc.,1995-96.
[c] Once daily dosing unless specified otherwise
[d] IR = immediate release; SR = sustained release

Appendix 3. Calcium Channel Blockers (CCBs)[a,b]

CCBs[c]	DOSE [d,e]	COMMENTS/CAUTIONS
Verapamil IR **Verapamil SR**	120-360 mg/day (in 2-3 divided doses) 120-360 mg/day (once daily or 2 divided doses)	• Verapamil is the preferred CCB for stage 1 HTN • Monitor for bradycardia and heart block • Contraindicated in AV node dysfunction (2nd or 3rd degree heart block), systolic CHF and decrease LV function • Doses > 240 mg/d tend to increase side effects with minima added benefit
Dihydropyridines[f] Amlodipine Felodipine Nicardipine SR Nifedipine XL/CC Nisoldipine	 5-10 mg/day elderly initial = 2.5 mg/day 2.5-10 mg/day 60-120 mg/day (in 2 divided doses) 30-90 mg/day 20-60 mg/day elderly initial = 10mg/day	• Short-acting nifedipine should not be used for essential HT • Monitor adverse effects: potent vasodilators can cause ankl edema, dizziness, flushing, headache • With the exception of amlodipine, use cautiously in CHF
Diltiazem IR **Diltiazem SR** Cardizem SR® Cardizem CD® Dilacor XR® Tiazac TZ®	90-360 mg/day (in 3-4 divided doses) 120-360 mg/day (in 2 divided doses) 180-360 mg/day 180-480 mg/day elderly may respond to 120 mg/day 120-540 mg/day	• Long acting preparations may be used for patients with a of the following: atrial arrhythmia, sinus tachycardia, and/ angina or asymptomatic ischemia • Monitor heart rate, may decrease sinus rate and cause heart block

[a] Adapted from Calcium channel blocking agents. In: Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1994:148v-150b.

[b] Semla TP, Beizer JL, Higbee MD, eds. APhA Geriatric Dosage Handbook. 2nd ed. Hudson: Lexi-Comp Inc.,1995-96.

[c] IR= immediate release formulation; SR= sustained release formulation; XL= Procardia® XL; CC= Adalat ® CC; CD= 24 hour continual release;
XR= extended release formulation; TZ= 24-hr preparation

[d] Once daily dosing unless otherwise specified

[e] For all CCB, use caution when used in patients with liver and renal dysfunction; monitor effect and adjust dose when appropriate

[f] Due to recent studies, isradapine has not been included until the issue of safety can be further addressed

Appendix 4. ACE Inhibitors (ACEIs)[a,b]

ACEI	DOSE[c]	COMMENTS/CAUTIONS
Benazepril	10-40 mg/day If CrCl < 30 mL/min, initial = 5 mg/day	• Monitor for hyperkalemia • Obtain baseline serum potassium, creatinine, and BUN, repeat labs within 2 weeks after initiating; discontinue ACEI if significant elevation occur • Avoid other potassium-sparing medications
Captopril	50-150 [d,e] mg/day (in 2-3 divided doses) elderly initial = 12.5 mg/day	
Enalapril	5-40 mg/day If CrCl < 30 mL/min, initial = 2.5 mg/d	
Fosinopril	10-40 [f] mg/day	
Lisinopril	10-40 mg/day If CrCl 10-30 mL/min, initial = 5 mg/d	
Moexapril	7.5-30 [e] mg/day If CrCl< 40 mL/min, initial = 3.75 mg/day max renal dose = 15 mg/day	
Quinapril	10-80 mg/day If CrCl 30-60 mL/min, initial = 5 mg/day If CrCl 10-30 mL/min, initial = 2.5 mg/day	
Ramipril	2.5-20 mg/day If CrCl < 40 mL/min, initial = 1.25 mg/day	
Trandolapril	2-8 [g]mg/day If CrCl < 30 mL/min, initial = 0.5 mg/day	

[a] Adapted from Antihypertensive: Angiotensin converting enzyme inhibitor.. In: Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri:
Facts and Comparisons Inc., 1996: 164h-165p.

[b] Semla TP, Beizer JL, Higbee MD, eds. APhA Geriatric Dosage Handbook. 2nd ed. Hudson: Lexi-Comp Inc.,1995-96.

[c] For most ACEIs (except captopril) once daily dosing is usually adequate. In selected instances the manufacturer recommends dividing doses when
the trough effect is inadequate. Note that the manufacturer of lisinopril and of trandolapril do not mention dividing doses.

[d] In general, higher dose than 150 mg/d of captopril are not used for HTN

[e] Patients should take 1 hour prior to food (empty stomach)

[f] Doses higher than 40 mg/d potentially increase side-effects with minimal additional BP control

[g] Manufacturer recommends starting dose of 1 mg/d for patients not receiving a diuretic in non-African American patients and 2 mg/d in African American patients

Appendix 5. Other Agents[a,b]

AGENT	DOSE[c]	COMMENTS/CAUTIONS
α BLOCKERS		•Monitor BP for orthostatic hypotension •Initial doses should be given q hs to reduce risk of syncope •Use cautiously in elderly due to first dose syncope or dizziness •Avoid in volume depleted patients due to orthostasis •Decrease in LDL and increases in HDL have been seen, but clinical significance unknown
Doxazosin	2-8 mg/day elderly initial = 1 mg max = 16[d] mg/day	
Prazosin	1-15 mg/day (in 2-3 divided doses) max = 20 mg/day	
Terazosin	1-5 mg/d (once daily or 2 divided doses) initial dose = 1 mg q hs max = 20 mg/day	
ANGIOTENSIN II ANTAGONIST		•Initiate dose of 25 mg in patients with possible depletion of intravascular volume (e.g. diuretics) and in hepatic impairment •Reserve for patients who have an indication for an ACEI, but who cannot tolerate it
Losartan	50-100 mg/day (once daily or 2 divided doses)	
CENTRALLY ACTING		•Taper dose to discontinue; do not discontinue suddenly •Antihypertensive effects of the patch are not seen until 2-3 days later; when switching from oral clonidine to a patch the oral dose should be gradually tapered down over 2-3 days while the patch is first administered •Clonidine patches are costly, but may be useful in selected patients •Monitor for sedation (usually transient) during initial therapy with methyldopa or whenever the dose is increased
Clonidine tablet	0.1-0.8[e] mg/d (in 2-3 divided doses)	
Clonidine TTS patch	0.1-0.6 mg patch weekly	
Methyldopa	500 [f] mg-3g/d (in 2-4 divided doses)	
PERIPHERALLY ACTING		•Monitor for sedation, depression, nightmares, tremors, nasal congestion •Higher doses than listed are associated with increase incidence of depression
Reserpine	0.1-0.25 mg/d	
VASODILATING AGENTS		•Monitor for reflex tachycardia with worsening angina, and edema •Monitor for headache and SLE (dose related) with hydralazine •Monitor for hypertrichosis, pericardial effusions with minoxidil •Minoxidil or hydralazine should be use with diuretic and β-blockers to reduce reflex tachycardia and edema
Minoxidil	5-40 mg/d (once daily or 2 divided doses)	
Hydralazine	40-200 mg/d (in 2-4 divided doses) initial dose = 10 mg qid elderly initial = 10 mg bid-tid	

[a] Adapted from. Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1996: 160-164g & 165q-165v.

[b] Semla TP, Beizer JL, Higbee MD, eds. APhA Geriatric Dosage Handbook. 2nd ed. Hudson: Lexi-Comp Inc., 1995-96.

[c] Once daily dosing unless specified otherwise

[d] Doses > 8 mg/d may increase side effects with little added benefit

[e] Maximum dose may be as high as 2.4 mg/d

[f] Initial therapy is usually 250 mg given 2-3 times a day in the first 48 hours; maintenance dose is usually given in 2 divided doses

Appendix 6a. Common Drug Interactions with Antihypertensive Agents[a-e]

DRUG CLASS	INTERACTING DRUG	DESCRIPTION
DIURETICS		
	ACEI	↑ hypotensive effect in the presence of intensive diuretic therapy due to sodium depletion and hypovolemia; at low doses this combination may be used synergistically
	Bile Acid Resins	↓ absorption of all diuretics; take diuretics 1 hour prior or 4 hours after bile acid resin
	Digoxin	All diuretics may induce hypokalemia which may ↑ risk of digitalis toxicity
	Lithium	With thiazide, a compensatory ↑ in proximal tubule reabsorption of sodium occurs, which results in ↑ lithium reabsorption; furosemide appears to have little effect in most people
	NSAIDs	NSAIDs ↓ antihypertensive effect when used with thiazides due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction
	Oral hypoglycemics	Thiazides may ↓ hypoglycemic effects of sulfonylureas possibly due to ↓ insulin sensitivity, ↓ insulin secretion or ↑ in K^+; clinical significance unclear
	K^+ preparations ACEI, NSAIDs	K^+sparing diuretics used concomitantly may ↑ K^+ serum levels
βeta-BLOCKERS		
	Cimetidine	Hypotension and bradycardia have been reported with propranolol and metoprolol when used with cimetidine due to ↑ serum levels of β-blockers that undergo hepatic metabolism
	Diltiazem Verapamil	Combination may potentiate the pharmacologic effects of β-blockers; additive effects on cardiac conduction
	Epinephrine	non-cardioselective agents may ↑ the pressor response resulting in ↑ in HTN/ bradycardia
	Lidocaine	↑ toxicity due to reduced lidocaine hepatic metabolism
	NSAIDs	NSAIDs ↓ antihypertensive effect due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction
	Neuroleptics	Some β-blockers and neuroleptics (chlorpromazine/thioridazine) may ↑ the plasma concentrations of one another; monitor for enhanced effects of both drugs
	Oral hypoglycemics	With non-cardioselective agents, ↓ hypoglycemic may occur possible due to inhibition of insulin secretion; also mask symptoms of hypoglycemia; clinical significance unclear
	Prazosin	↑ postural hypotension due to ↓ compensatory cardiovascular response
	Propafenone	↑ hypotensive effect has been seen with propranolol and metoprolol due to inhibition of metabolic clearance; heart failure and nightmares have been reported
	Rifampin	May enhance the hepatic metabolism of propranolol and metoprolol; enzyme induction effect may resolve after a 3-4 week washout period
	Theophylline	↑ serum concentration in a dose-dependent manner has been seen with propranolol
CCB		
	Carbamazepine	↑ toxicity has been noted with verapamil and diltiazem use due to reduced metabolism of carbamazepine; interaction more significant with verapamil
	Cimetidine	Metabolism has been ↓ especially with verapamil, diltiazem, nifedipine
	Cyclosporin	Blood concentrations have increased with verapamil, diltiazem and nicardipine; renal toxicity has been reported
	Digoxin	Verapamil, diltiazem, bepridil, nisoldipine have ↑ digoxin levels by 20-70%
	Lithium	Combination use with verapamil or diltiazem may result in neurotoxicity which may occur without attendant increase in serum level
	Quinidine	Verapamil inhibits metabolism of quinidine leading to ↑ toxicity; nifedipine appears to reduce blood concentrations although mechanism unknown
	Theophylline	Inhibition of hepatic metabolism with verapamil may lead to increase serum levels

[a] Adapted from JNC V [14]

[b] Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1996.

[c] Mignat C, Unger T. ACE inhibitors. Drug interactions of clinical significance. Drug Safety 1995 May 12(5):334-47.

[d] Hansten PD, Horn JR eds. Drug interactions & Updates, Vancouver: Applied Therapeutics, Inc., 1993.

[e] **Bold** serious drug interaction; *Italics* = moderate; Regular = minor **;**NSAIDs=nonsteroidal anti-inflammatory drug; GFR=glomerular filtration rate; K^+ =potassium; ACEI=angiotensin converting enzyme inhibitor; PG=prostaglandin

Appendix 6b. Common Drug Interactions with Antihypertensive Agents[a-e]

DRUG CLASS	INTERACTING DRUG	DESCRIPTION
ACEI		
	Lithium	↑ toxicity; suggested mechanism is ACEI induced sodium depletion resulting in ↑ reabsorption
	NSAIDs	NSAIDs ↓ antihypertensive effects due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction
	K^+ preparations K^+-sparing diuretics	Concomitant therapy may ↑ K^+ serum levels
α-BLOCKERS		
	β-blockers	Prazosin may ↑ postural hypotension due to ↓ compensatory cardiovascular response
	Indomethacin	May ↓ antihypertensive action with prazosin due to inhibition of PG synthesis
	Verapamil	May cause greater hypotensive effect with prazosin or terazosin than with either drug alone
ANGIOTENSIN II ANTAGONIST		
	Cimetidine	Coadministration led to an ↑ of about 18% in the area under the curve (AUC) of lorsartan, but did not affect the pharmacokinetics of its active metabolite
	Phenobarbital	Coadministration led to a reduction of about 20% in the AUC of lorsartan and that of its active metabolite
CENTRALLY ACTING		
	β-blockers	The severity of withdrawal HTN caused by abrupt discontinuation of clonidine may be greater in patients taking β-blockers possibly due to unopposed α-adrenergic stimulation; methyldopa and β-blockers may rarely cause paradoxical HTN
	Levodopa	Methyldopa may enhance the therapeutic response to levodopa
	Lithium	↑ lithium toxicity has been reported with methyldopa use in a few patients
	Sympathomimetics	Methyldopa may potentiate the pressor effects and lead to HTN
	TCA	May inhibit the antihypertensive response of clonidine; mechanism not established
PERIPHERALLY ACTING		
	Sympathomimetics	Concurrent use with reserpine may prolong effects of direct-acting sympathomimetics (epinephrine); concurrent use with indirect-acting sympathomimetics (ephedrine) may inhibit effects
	TCA	Concurrent use with reserpine may ↓ antihypertensive effects
VASODILATORS		
	Indomethacin	↓ antihypertensive effect of hydralazine due to prostaglandin synthesis inhibition
	Propranolol Metoprolol	Serum levels of propranolol or metoprolol may be ↑ with hydralazine use; clinical significance unknown

[a] Adapted from JNC V [14]

[b] Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1996.

[c] Mignat C, Unger T. ACE inhibitors. Drug interactions of clinical significance. Drug Safety 1995 May 12(5):334-47.

[d] Hansten PD, Horn JR eds. Drug interactions & Updates, Vancouver: Applied Therapeutics, Inc., 1993.

[e] **Bold** serious drug interaction; *Italics* = moderate; Regular = minor ;ACEI=angiotensin converting enzyme inhibitor; PG=prostaglandin

Appendix 7. Selected Costs for Hypertension Drug Therapy (as of November 1996)

For current prices, check Drug & Pharmaceutical Product Management Bulletin Board # 708-531-7947

DRUG	DOSE[a]	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
DIURETICS		
Thiazides		
Chlorthiazide	1000 mg qd	
Hydrochlorothiazide	25 mg qd	$ 0.09
HCTZ/Triamterene	50 mg/75 mg qd	$ 0.61
Thiazide-Related		
Chlorthalidone	25 mg qd	$ 0.29
Indapamide	2.5 mg qd	$ 3.52
Metolazone		
Mykrox ®	0.5 mg qd	$ 12.90
Zaroxolyn ®	5 mg qd	$ 8.19
Loop Diuretics		
Furosemide	40 mg qd	$ 0.19
Bumetanide	2 mg qd	$ 3.87
Torsemide	10 mg qd	$ 8.04
BETA BLOCKERS		
Non-cardioselective		
Propranolol	IR: 40 mg bid	$ 0.29
	SR: 80 mg bid	$ 16.76
Cardioselective		
Atenolol	50 mg qd	$ 0.52
Metoprolol	50 mg bid	$ 1.39
Acebutolol	200 mg bid	$ 12.34
α & β Blocking Agents		
Labetalol	200 mg bid	$ 12.34
CALCIUM CHANNEL BLOCKERS		
Verapamil IR	120 mg bid	$ 1.82
Verapamil SR	240 mg qd	$ 7.05
Dihydropyridines		
Amlodipine	5 mg qd	$ 18.64
Felodipine	10 mg qd	$ 14.39
Nicardipine SR	30 mg bid	$ 9.57
Adalat CC®	90 mg qd	$ 13.50
Procardia XL®	90 mg qd	$ 34.03
Nisoldipine	20 mg qd	$ 14.21
Diltiazem IR	60 mg tid	$ 3.38
Cardizem SR®	120 mg bid	$ 32.55
Cardizem CD®	240 mg qd	$ 28.32
Dilacor XR®	240 mg qd	$ 15.56
Tiazac®	240 mg qd	$ 16.66

[a] Usual doses; does not reflect equivalent doses

Appendix 7. Selected Costs for Hypertension Drug Therapy continued (as of November 1996)

For current prices, check Drug & Pharmaceutical Product Management Bulletin Board # 708-531-7947

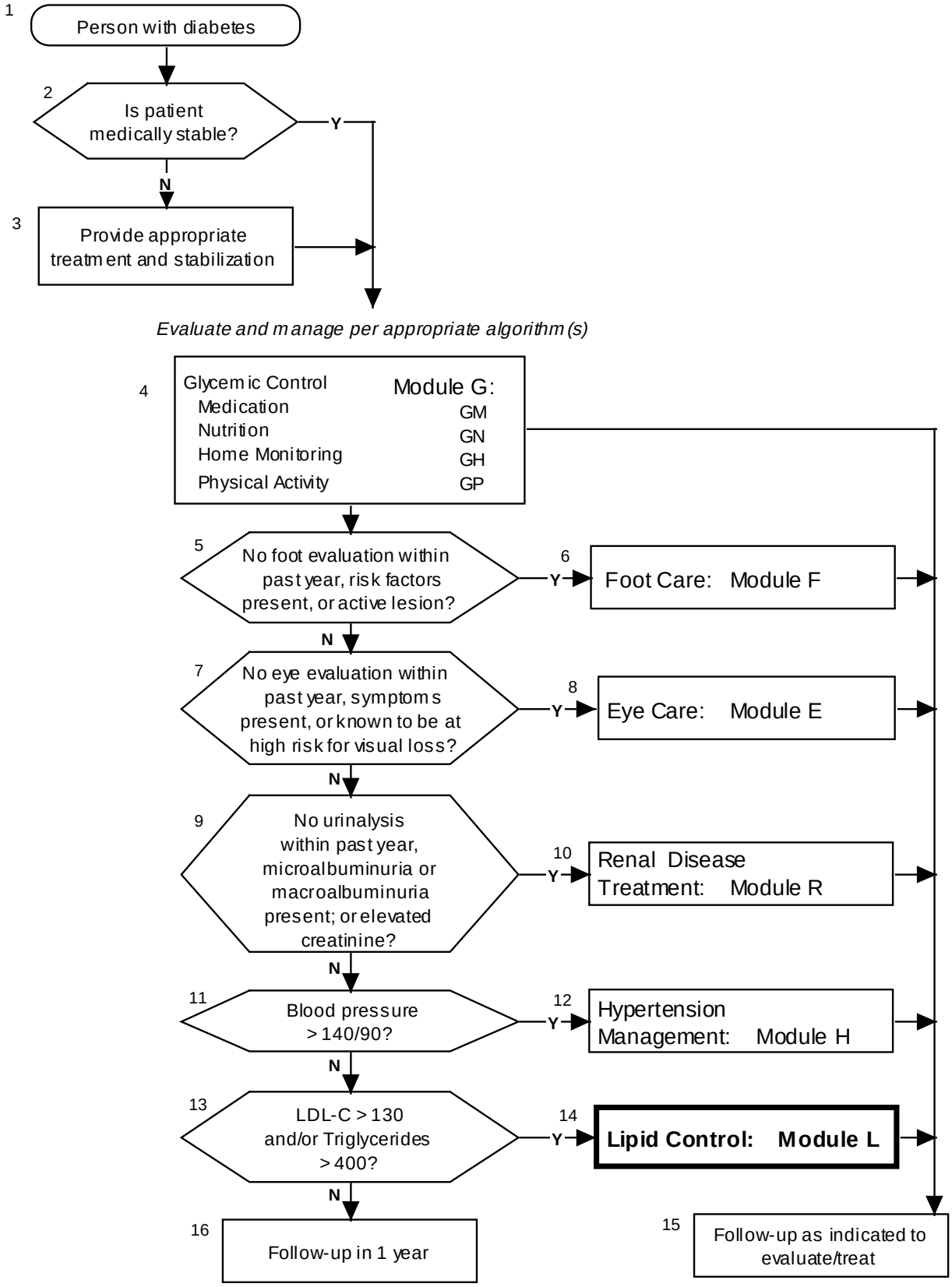
DRUG	DOSE[a]	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
ACE INHIBITORS		
Captopril	25 mg bid	$ 1.09
Benazepril	20 mg qd	$ 7.38
Enalapril	10 mg bid	$ 28.41
Fosinopril	20 mg qd	$ 7.48
Lisinopril	20 mg qd	$ 7.80
Moexapril	15 mg qd	$ 7.05
Quinapril	20 mg qd	$ 7.38
Ramipril	10 mg qd	$ 8.44
Trandolapril	4 mg qd	$ 8.70
α BLOCKERS		
Doxazosin	4 mg qd	$ 15.89
Prazosin	2 mg bid	$ 1.02
Terazosin	5 mg qd	$ 13.50
ANGIOTENSIN II ANTAGONIST		
Losartan	50 mg qd	$ 17.79
CENTRALLY ACTING		
Clonidine Tablet	0.2 mg bid	$ 0.43
Clonidine Patch	TTS-2 q week	$ 29.91
Methyldopa	500 mg tid	$ 4.23
PERIPHERALLY ACTING		
Reserpine	0.1 mg qd	$ 0.60
VASODILATING AGENTS		
Minoxidil	10 mg qd	$ 2.01
Hydralazine	25 mg tid	$ 0.57

[a] Usual doses; does not reflect equivalent doses

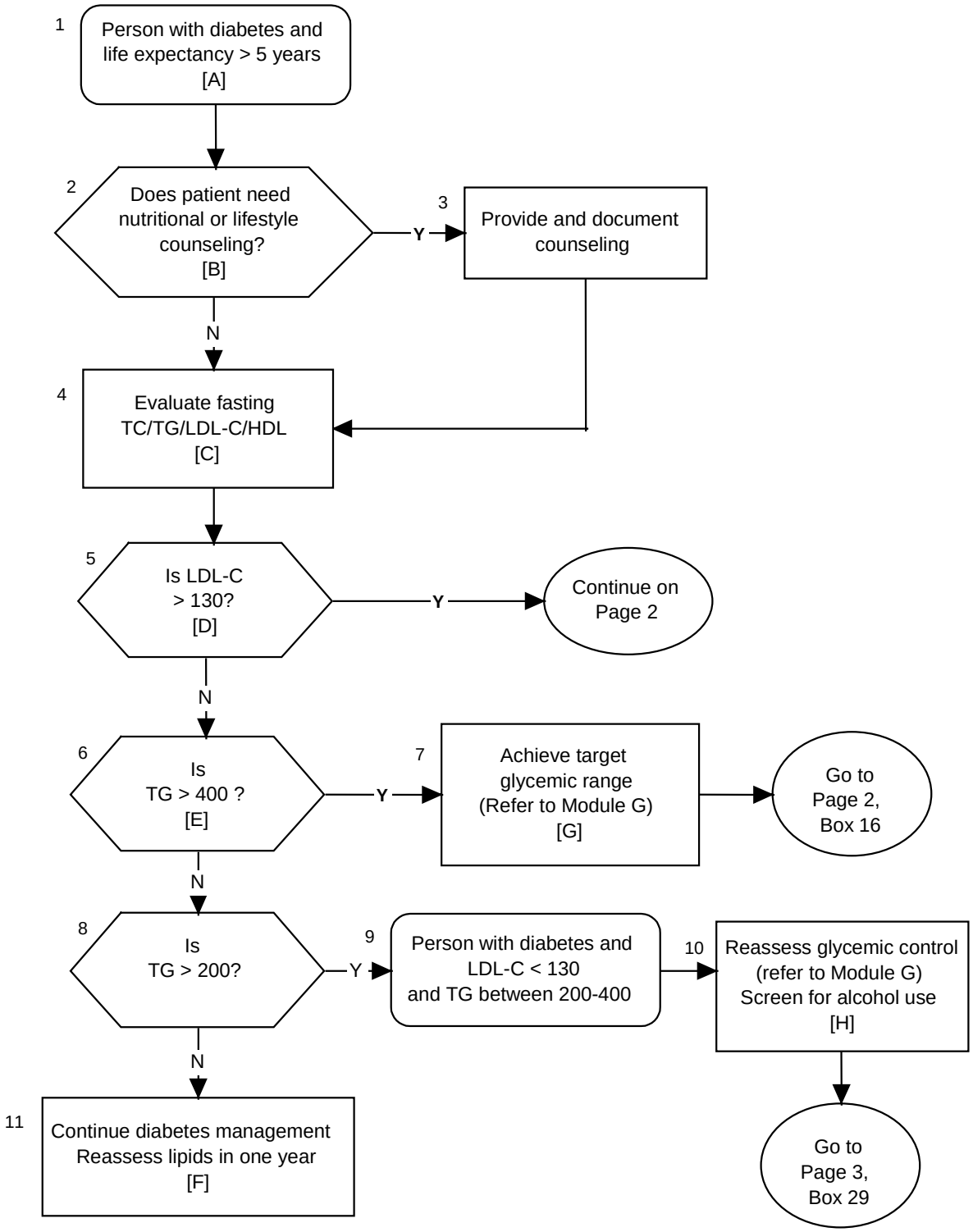
Module L

Lipid Control

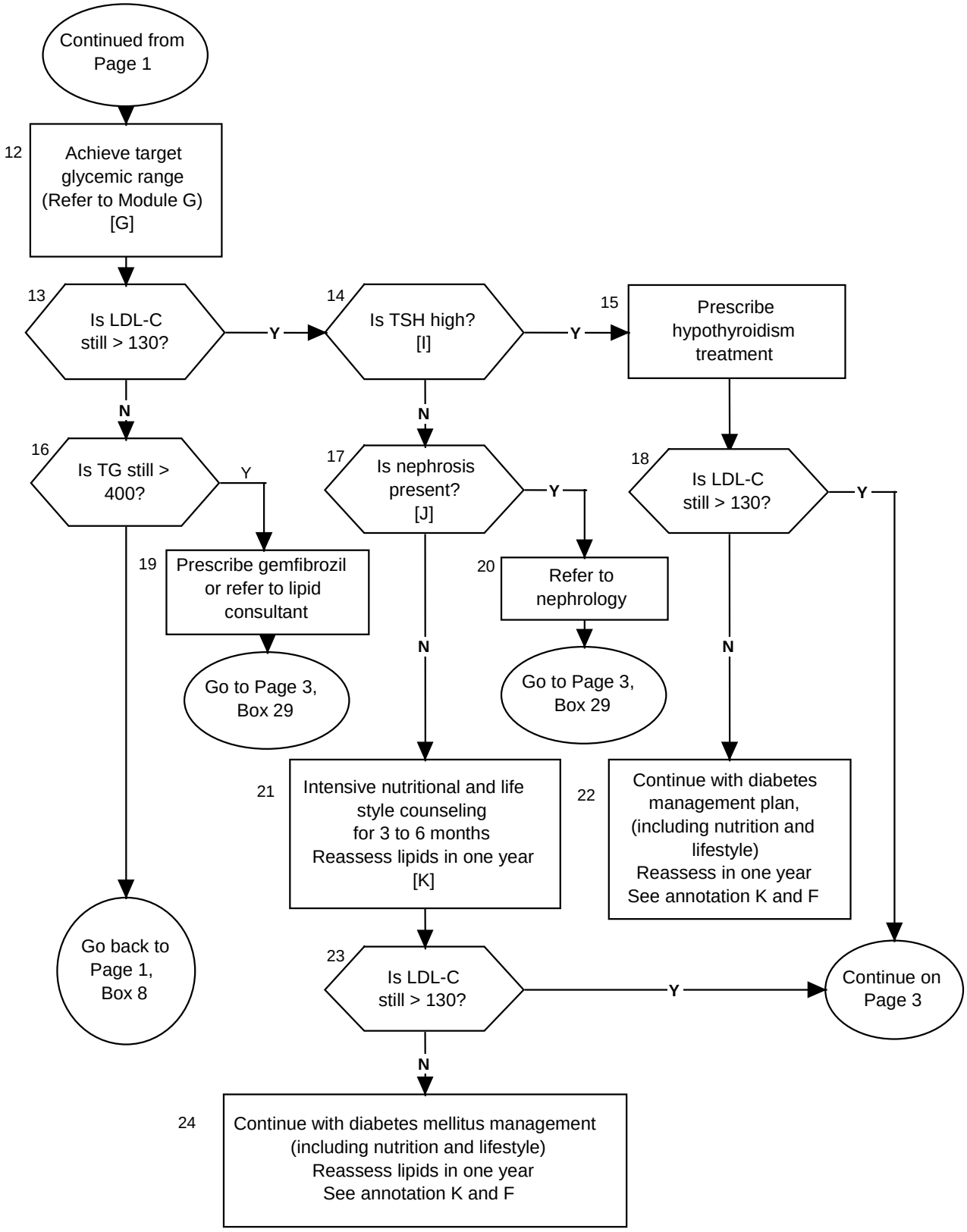
Management of Diabetes Mellitus



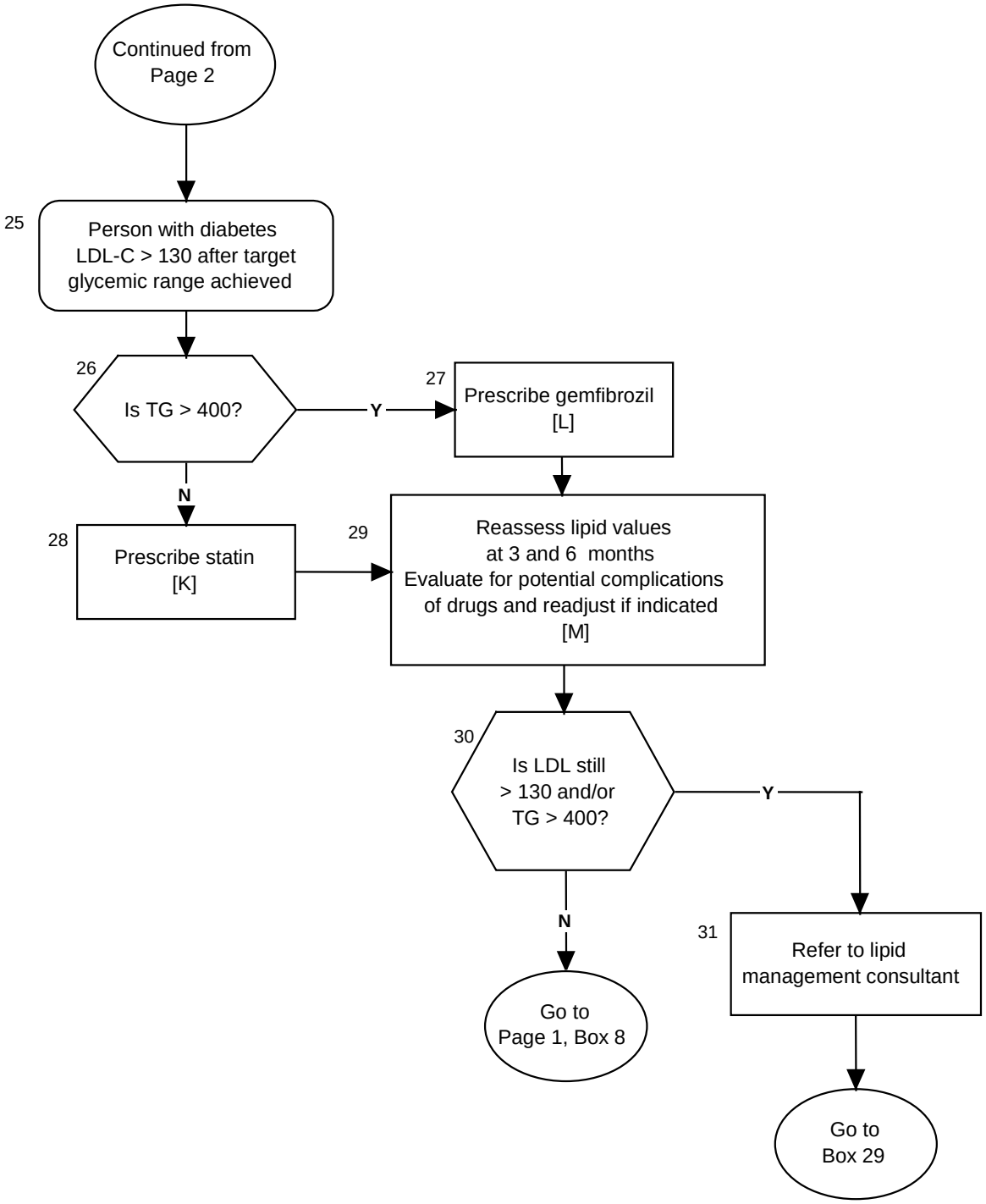
Management of Diabetes Mellitus
Lipid Control



Management of Diabetes Mellitus
Lipid Control



Management of Diabetes Mellitus
Lipid Control



Module L

Lipid Control

ANNOTATIONS

MANAGEMENT OF DIABETES MELLITUS

Lipid Control Annotations

Module L

A. Person with Diabetes and Life Expectancy > 5 Years — It is unlikely that there will be benefit to the patient of treating dyslipidemia unless the patient lives a reasonable number of years; 5 years is chosen as a guideline. There is no significant correlation between total serum cholesterol and CHD in persons above age 70 years (Krumholz 1994); however, intervention trials suggest a small attributable benefit to lowering total cholesterol in persons above 70.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Absence of a relationship between serum cholesterol level and CHD/mortality > age 70 years	Krumholz et al. (1994)	I	B

B. Provide Appropriate Nutritional and Lifestyle Counseling

1. Regular Physical Activity

   a. Minimum Goal

   - Regular physical activity
   - Small increase over current level
   - Progression to level that achieves cardiovascular fitness (e.g., 30 minutes of brisk walking most days of the week)
   - Muscular strengthening and joint flexibility

   b. Recommendations

   (1) Essential components of a systematic, individualized exercise prescription include the appropriate mode, intensity, duration, frequency, and progression of physical activity.

   (2) Assess risk, preferably with exercise test to guide prescription.

   (3) Advise medically supervised programs for moderate to high-risk patients.

(4) Consider level of fitness, medications that may influence heart rate, risk of cardiovascular or orthopedic injury, individual preferences, and individual program objectives.

(5) Encourage minimum of 30 to 60 minutes of moderate intensity activity, 3 to 4 times weekly (e.g., walking, jogging, cycling or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, using stairs, gardening, household work). Minimum benefit, 5 to 6 hours per week.

(6) Light to moderate physical activity requires sustained, rhythmic muscular movements, is equivalent to sustained walking, performed at less than 60% of maximum heart rate for age. Maximum heart rate equals roughly 220 beats per minute minus age.

2. Smoking Cessation

a. Goal

- Complete cessation

b. Recommendations

(1) A cigarette smoker is defined as having smoked at least 100 cigarettes and currently smokes cigarettes.

(2) Regular exposure to tobacco smoke is defined as the occurrence of tobacco smoking anywhere in the home for more than 3 days each week.

(3) A smokeless tobacco user is defined as having snuffed or chewed tobacco at least 20 times and currently uses snuff or chewing tobacco.

(4) Every person who smokes should be offered smoking cessation treatment at each visit.

(5) Ask and record the tobacco-use status of every patient.

(6) Cessation treatment as brief as 3 minutes is effective.

(7) The more intense the treatment, the more effective the abstinence.

(8) Nicotine replacement therapy (nicotine patches or gum), clinician-delivered social support, and skills training are effective components of smoking cessation treatment.

3. Stress Management

a. Goal

- Understand and modify stress

b. Recommendations

(1) Ways to cope with stress: Relax, emergency stress stoppers, exercise, reduce chemical stresses.

(2) Stress management skills: Avoid, adapt, alter; speaking up; and time management.

4. Alcohol Counseling

a. Goals

- Screen to detect problem drinking
- Screen to detect hazardous drinking

b. Recommendations

(1) Ask patients to describe the quantity, frequency, other characteristics of their use of wine, beer, and liquor, including frequency of intoxication and tolerance of the effect of alcohol.

(2) Suggested safe drinking — 2 drinks per day in men and 1 drink per day in women. One drink is defined as 12 ounces of beer, one 5-ounce glass of wine, or 1.5 fluid ounces (one jigger) of distilled spirits.

(3) Referral to alcohol treatment program if evidence of problem or hazardous drinking.

(4) At risk is defined as 5 drinks per day in men, 3 drinks per day in women, or frequent intoxication.

(5) Heavy drinking is defined as 5 or more drinks, once or twice each weekend.

(6) Persons who drink should be informed of the dangers of driving or other potentially dangerous activities after drinking.

(7) Use of alcohol should be discouraged in persons younger than the legal age for drinking.

5. Basic Nutrition Counseling

a. Referral to Registered Dietitian for individualized instruction in meal planning, lifestyle modifications, and potential food/drug interactions if applicable. Referral may include those patients with:

- Newly diagnosed diabetes
- Diabetes out of control
- Diet related complications
- Type I diabetes
- Insulin pump
- Multiple daily injections

b. Goal — Fat, cholesterol, and sodium consumption follow nutrition recommendations:

- Adhere to appropriate meal pattern, exercise and medication treatment plan to maintain blood glucose and lipids within target range and to keep electrolytes within normal range
- Maintain kidney function and/or slow progression of disease
- Maintain nutrition health

c. Recommendations — Eat a variety of foods daily:

(1) Five servings of fruits and vegetables; six servings of breads, cereals, or legumes each day; two servings each of low fat dairy and meat products; and use fat sparingly.

(2) Calories to achieve or maintain reasonable weight (25-35 calories per kg/body weight balanced with energy expenditure).

(3) Encourage weight loss as appropriate.

(4) Limit alcohol to equal to or less than 2 drinks a day.

(5) Discuss role and effect of diet, weight loss or maintenance, physical activity, smoking cessation, medications, hypertension, and renal disease.

d. Hyperlipidemia:

(1) Fats restricted according to risk factors and severity of serum lipid levels.

(2) Emphasize consumption of fish, poultry prepared without skin, lean meats, and low fat dairy products.

(3) Emphasize monounsaturated fats as preferred fat (e.g., olive, canola, peanut, or avocado oil).

(4) Step I: Fat < 30% total calories (10% monounsaturated fat, 10% saturated fat), < 300 mg cholesterol.

(5) Step II: Fat < 20% total calories (10% monounsaturated fat, 7% saturated fat), < 200 mg cholesterol.

(6) If triglycerides < 200 mg/dL, ensure blood glucose is under control; limit alcohol and simple sugars intake.

e. Hypertension:

(1) Limit sodium intake to < 2,300 mg/day and avoid the following:

- Salty or highly processed foods such as smoked, cured or highly salted meats
- Bouillon and regular canned soups
- Commercial products with high salt content
- Foods processed in brine
- Salt seasonings and sauces

(2) Maintain or increase foods high in potassium, or if applicable, per medication.

f. End Stage Renal Disease:

(1) Protein intake based on 10% of total calories:

- Decrease meat and dairy portions
- Diabetic nephropathy, restrict to 0.8 g/kg

(2) Individualize sodium, potassium, phosphorus, and calcium:

- Recommend more vegetables (3-5 servings/day) ingestion
- Recommend moderate amounts of fruits (2-4 servings/day) consumption

(3) Vitamin/mineral supplement as recommended by health care provider

6. Intensive Nutrition Counseling, Referral for Nutrition Counseling — Referral to Registered Dietitian for individualized instruction in meal planning, lifestyle modifications, and food/drug interactions if applicable.

a. Referral may include those patients with newly diagnosed diabetes such as:

- Diabetes out of control
- Diet related complications
- Type I diabetes
- Insulin pump
- Multiple daily injections

b. Goal

- Fat, cholesterol, and sodium consumed follow nutrition prescription.

- Adhere to appropriate meal pattern, exercise, and medication treatment plan to:

  — Maintain blood glucose and lipids within target range, and keep electrolytes within normal range

  — Maintain kidney function and/or slow progression of disease

  — Maintain nutrition health

c. Recommendations

(1) Adjust goals and/or nutrition prescription.

(2) Review records and evaluate adherence and understanding of:

- Percent fat intake and type of fat
- Protein intake
- Carbohydrate intake
- Soluble fiber intake
- Physical activity
- Alcohol intake
- Tobacco consumption

(3) Provide self-management training and material.

(4) Assess change in weight, tobacco habit, physical activity, medications, and laboratory values.

(5) Review educational materials on:

- Food labeling
- Recipe modification
- Soluble fiber
- Weight reduction, if applicable
- Dining out
- If changes in medication, potential food/drug interaction

C. Evaluate Fasting TC/TG/LDL-C/HDL — These lipids must be measured in the fasting state because serum triglycerides (TG) are affected by meals and, if elevated above about 400 mg/dL, interfere with the calculation of HDL-cholesterol (HDL-C). Below this TG value, the calculation works reasonably well (Demacker et al. 1996; Nauck et al. 1996; Whiting et al. 1997). If the TG level is > 400 mg/dL, the calculation will not work and either a specific assay for LDL-C must be obtained or the raised TG lowered by treatment and the measurements redone.

If measurements of LDL-C and HDL-C are not available, serum total cholesterol can be measured in the fed or fasting state; however, the recommendation here is to measure LDL-C.

The reason for measuring serum lipids in Type II diabetes is because dyslipidemia is common (Laakso, 1996) and a raised level of serum cholesterol is as powerful a risk factor for coronary heart disease (CHD) in patients with Type II diabetes as it is in non-diabetics (Pyorala, & Steiner, 1996). A major problem is that there are no data to show that reversal of dyslipidemia in Type II diabetes results in primary prevention of CHD (Laakso, 1996), and only post-hoc subgroup analysis from larger trials (4S, CARE) suggests that it leads to secondary prevention of a second CHD event (Kreisberg, 1996; Sacks et al. 1996). There may be benefit of a global program that addresses serum cholesterol, smoking, and hypertension, with the use of aspirin, in men under age 60 years but these approaches may have less effect in Type II diabetes than non-diabetics (Krolewski et al. 1996). It is known that lipid-lowering therapies are effective at lowering serum cholesterol in Type II diabetes (Behounek et al. 1994; Sweany et al. 1995). On balance, it is reasonable to conclude that one can use about the same approach to dyslipidemia in Type II diabetes as in those without Type II diabetes until large-scale diabetes-specific data are available. See Attachment 1, Drugs that alter plasma lipids from the VHA Pharmacy Benefits Management Medical Advisory Panel Guidelines at the end of this chapter. Also, refer to Attachments 2 and 3, Drug Interactions and Costs for Hyperlipidemia Drug Therapy.

In persons without diabetes there is benefit of lowering serum cholesterol in both primary (Pedersen 1994) and secondary prevention of CHD (Sacks et al. 1996; Shepherd et al. 1995).

> **Note:** This algorithm does not address the issue of a low HDL-C without a raised LDL-C because niacin, which is effective at raising the low HDL-C, should be avoided in Type II diabetes (see annotation D) and gemfibrozil, which can also

raise HDL-C, is currently under study in a VA Cooperative Study to see if CHD outcomes are actually affected.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Friedewald calculation of LDC-cholesterol	Demacker et al. (1996) Whiting et al. (1997)	I B	B B
Serum cholesterol as a risk factor for CHD in Type II diabetes	Pyorala & Steiner 1996	I	C
Lowering serum cholesterol in Type II benefits CHD	Sacks et al. (1996) Pyorala et al. (1997)	IIa I	B B
Lipid therapies decrease raised serum cholesterol in Type II diabetes	Behounek et al. (1994) Sweany et al. (1995)	I	A

D. **Is LDL-C > 130?** — There are no data for persons with diabetes (Sacks et al. 1996; Pedersen, 1994; Shepherd et al. 1995) as to the lower limit of LDL-C below which there is no further efficacy in decreasing cardiovascular events or mortality. However, in persons without diabetes but with a recent (3 months to 20 months) history of myocardial infarction, the treatment benefit decreased to zero as the LDL-C level approached 125 mg/dL. Based upon this result, the cutpoint for treatment for either primary or secondary prevention should be set at 125-130 mg/dL, unless a person has had coronary bypass surgery. In this group of individuals (Post Coronary Artery Bypass Graft Trial Investigators), aggressive lowering of LDL-C levels to below 100 mg/dL reduced the progression of atherosclerosis in grafts. However, the study was not designed to have adequate power to detect treatment-related differences in clinical events. There was no significant difference in composite and points (death, nonfatal myocardial infarction, or stroke), although there was a nonsignificant trend (p=0.03) towards fewer revascularization procedures.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Little evidence of further benefit in lowering serum LDL-C < 130 mg/dL in non-Type II diabetes patients	Sacks et al. (1996) Pedersen 1994 Shepherd et al. (1995)	I I I	A A A
Benefit of lowering LDL-C levels to < 100 mg/dL in individuals with coronary bypass surgery grafts	Post Coronary Artery Bypass Trial Investigators 1997	I	A

E. **Is TG > 400?** — These cut-off points for taking action on the raised TG levels at this point rather than later were chosen because treatment is likely to be needed no matter what happens after nutrition, lifestyle, and LDL-C values are addressed; less raised values of TG are likely to revert toward normal after these maneuvers. Fasting specimen should be 12-14 hours prior to blood drawing.

F. **Continue Diabetes Management, Reassess Lipids in One Year** — The following evaluation of the patient at follow-up visits is from the VA Medical Advisory Panel Pharmacologic Guidelines for Treatment of Patients with Hyperlipidemia.

1. History

    a. Diet compliance

    b. Medication compliance (if indicated) and presence of symptoms suggesting adverse drug reactions

    c. Current medications or pertinent changes in other drug therapy

    d. Compliance with exercise program if prescribed

    e. Reevaluation of the modifiable cardiovascular risk factors

    f. Presence of muscle aches in large muscle groups

2. Physical examination

    a. Weight

    b. Blood pressure if indicated

3. Laboratory tests

    a. Periodic fasting lipid profile

    b. Creatinine kinase (CK) if symptoms of myositis

    c. LFT's for patients on gemfibrozil, HMGCoA-RI's

4. Adverse event monitoring (including but not limited to):

    a. Significant elevations of liver enzymes (> 3 times the upper limit of normal) while on HMGCoA-RI, or gemfibrozil therapy

b. Symptoms of myositis while on gemfibrozil or HMGCoA-RI therapy alone or in combination with other drugs

G. Achieve Target Glycemic Range — Serum lipids can be abnormal simply because of poor glycemic control (Laakso, 1996). See glycemic control algorithm **(Module G)** for details.

H. Screen for Alcohol Use — Use of a standardized instrument (CAGE, NAST, AUDIT, etc) to screen for alcohol consumption is recommended. Alcohol excess can cause raised TG; efforts should be made to remedy this cause, if present. If excess alcohol is not present, or if uncertain, refer to lipid management consultant.

1. Moderation of Alcohol

a. Goals

- Screen to detect problem drinking
- Screen to detect hazardous drinking

b. Recommendations

(1) Ask patients to describe the quantity, frequency, other characteristics of their use of wine, beer, and liquor, including frequency of intoxication and tolerance of the effect of alcohol.

(2) Suggested safe drinking: 2 drinks per day in men and 1 drink per day in women. One drink is defined as 12 ounces of beer, one 5-ounce glass of wine, or 1.5 fluid ounces (one jigger) of distilled spirits.

(3) Referral to alcohol treatment program if evidence of problem or hazardous drinking.

(4) At risk is defined as 5 drinks per day in men, 3 drinks per day in women, or frequent intoxication.

(5) Heavy drinking is defined as 5 or more drinks, once or twice each weekend.

(6) Persons who drink should be informed of the dangers of driving or other potentially dangerous activities after drinking.

(7) Use of alcohol should be discouraged in persons younger than the legal age for drinking.

I. **Is TSH High?** — Values of serum TSH > 10 mU/L are clearly raised. Primary hypothyroidism, which becomes symptomatic at raised serum TSH levels of about 10 mU/L and can affect serum lipids at less elevated values, affects only a small number of those with raised serum cholesterol but is quite treatable. Screening for primary hypothyroidism in those without Type II diabetes is reasonably cost-effective (Danese et al. 1996) and this is probably true in Type II diabetes as well.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Screening for hypothyroidism is cost-effective	Danese et al. (1996)		B

J. **Is Nephrosis Present?**—Defined as 24-hour urine protein excretion greater than 2 grams.

K. **Intensive Nutritional and Lifestyle Counseling for 3 to 6 Months and Reassess in One Year** — A raised LDL-C may respond to more intensive lifestyle and nutritional therapy. More importantly, changes in lifestyle, e.g., smoking cessation, can decrease the global risk of CHD even without a change in the serum cholesterol level (Avins & Browner, 1996; Garber & Browner, 1996). This stratified approach targets the use of lipid-lowering drugs to those at higher risk (Ramsey et al. 1996), an approach which is particularly useful in view of the need for cost effectiveness and the uncertainty of translating efficacy ("it can work") to effectiveness ("it actually does work in practice") (Marchioli et al. 1996). See Annotation B for further details.

TABLE OF EVIDENCE

Variables	Reference	Strength of Recommendation	Level of Evidence
Lifestyle change can affect CHD outcome without changing serum cholesterol	Avins & Browner 1996		B
Appropriate stratification of the use of lipid lowering drugs	Ramsey et al. (1996)	IIa	**B**
"Efficacious" need not mean "effective" in actual practice	Marchioli et al. (1996)	I	B

L. **Provide Gemfibrozil** — The practitioner here has the choice of: (a) going on to the use of a "statin" drug and assessing the effect on the TG level before addressing the raised TG level directly OR (b) instituting therapy with gemfibrozil which will usually lower the raised TG.

Niacin, which is effective in lowering both a raised TG and a raised LDL-C, is avoided here because of its tendency to raise the serum glucose. However, it could be tried with caution in selected cases.

DRUG THERAPY*

* The following table is taken from the VHA Pharmacy Benefits Management/Medical Advisory Panel Pharmacologic Management of Hyperlipidemia

DRUG	EFFECT	DOSE	CAUTIONS/MONITOR	CONSIDERATIONS
gemfibrozil 600 mg tab	↓ TG 30-60% ↑ HDL 10-30% ± LDL 10%	600 mg bid 30 min. ac	LFT's If Cr Cl is 10-50 mL/min give 50% of dose; if < 10 give 25%[a]	
HMG CoA reductase inhibitors (HMGCoA-RI) **fluvastatin** 20,40 mg cap **lovastatin** 10,20,40 mg tab **pravastatin** 10,20,40 mg tab **simvastatin** 5,10,20,40mg tab	↓ LDL 25-45%[b] ↓ CHOL 15-30% ↑ HDL 5-15% ↓ TG 5-15%	LFT's ↑ in 0.6-1.3% Myalgia 1.8-2.7% Myopathy 0.1-0.5% -5% in combination with gemfibrozil -2% in combination with niacin	Add BAR to ↓ LDL-C up to 50% Pre-existing renal dysfunction may put a patient at higher risk for myopathy Evening/bedtime dosing may improve efficacy; lovastatin should be taken with the evening meal	Add BAR to ↓ LDL-C up to 50% Pre-existing renal dysfunction may put a patient at higher risk for myopathy Evening/bedtime dosing may improve efficacy; lovastatin should be taken with the evening meal

[a]Bennett WM, Aranoff AR, Morrison G, et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. *Am J of Kidney Diseases* 1983; 3(3):155-187.
[b]Depending on specific agent.

M. Reassess Initially in 1-3 Months and Evaluate for Potential Complications of Drugs. Evaluate Again at 4-6 and 8-10 Months — Firm data on the optimum frequency of follow-up do not exist. Because the response of LDL-C to statin drugs is partly dose-dependent, reassessment of the serum LDL-C in one to three months will help guide therapy. Further, most side effects of these drugs occur in the first few months. The main side effect, which occurs in two to three percent, is hepatic dysfunction; hepatic enzyme measurements once or twice in the first three months of therapy and every three or four months thereafter in the first year of therapy will generally detect this. If there is no hepatic dysfunction as a result of the drug, one can re-assay these enzymes once or twice a year. The much rarer muscle dysfunction due to these drugs (< 1%) is usually detected by complaints of muscle pain or soreness and raised muscle enzymes, especially creatinine kinase.

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ATTACHMENT 1

DRUGS THAT ALTER PLASMA LIPIDS[a]

DRUG	CHOL	TRIG	HDL-C	COMMENT
α–AGONISTS AND ANTAGONISTS (e.g., prazosin, doxazosin, clonidine)	↓ 0-10%	↓ 0-20%	↑ 0-15%	
β-BLOCKERS non-selective selective alpha blocking	 No change No change No change or ↓	 ↑ 20-50% ↑ 15-30% No change	 ↓ 10-15% ↓ 5-10% No change	I. transient effects; cardio-selective agents affect lipids less II. α–blocking or intrinsic sympathomimetic agents are lipid neutral
DIURETICS thiazides	↑ 5-7% initially ↑ 0-3% later	↑ 30-50%	↑ 13 mg/dL	I. effects may be transient
ESTROGENS Hormone Replacement Therapy (HRT)[b] Oral Contraceptive Pills (OCP) Monophasics Triphasics	 ---------- ↑ 5-20% ↑ 10-15%	 ↑ 10-15% ↑ 10-45% ↑ 10-15%	 ↑ Up to 9% ↑ 15- ↓ 15% ↑ 5-10%	I. HRT may ↓ LDL by 10-15%. OCP can ↑ CHOL and TRIG, mainly due to progestin component
Cyclosporine	↑ 15-20%	No change	No change	I. LDL-C ↑ by 30%
Ethanol	No change	↑ up to 50%		I. marked elevations may occur in hypertriglyceridemic patients II. modest ethanol (2 oz. / day) may ↑ HDL-C
Glucocorticoids	↑ 5-10%	↑ 15-20%	----------	
Isotretinoin	↑ 5-20%	↑ 50-60%	↓ 10-15%	I. reversible changes seen 8 weeks after stopping the drug

[a]Adapted from McKenney, JM. In: Koda-Kimble MA, Young LY eds. Applied Therapeutics: The Clinical Use of Drugs. 6th ed. Vancouver: Applied Therapeutics Inc., 1995:9-12.

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ATTACHMENT 2

DRUG INTERACTIONS [a,b]

PRECIPITANT AGENT	INTERACTIVE AGENT	CLINICAL MANIFESTATIONS OF DRUG INTERACTIONS	COMMENT
Gemfibrozil	Warfarin	• Risk of ↑ anticoagulant activity	
Bile Acid Resins (BAR's)	Digoxin Gemfibrozil Levothyroxine Phenobarbital Propranolol HMGCoA-RI's Thiazides Warfarin	• Can decrease the absorption of interactive agents	• Take other drugs 1 hour before or 4 hours after BAR
HMGCoA Reductase Inhibitors (HMGCoA-RI's)	Cyclosporine	• Risk of rhabdomyolysis or myopathy with concomitant use	• Recommend a dose reduction of lovastatin[a] to 20 mg/day or less • Recommend a dose reduction of simvastatin [c,d] to 10 mg/day or less • Limited trials have shown fluvastatin to be safe [e,f] • Pravastatin [g-i] has extensive data to recommend its use in this population
HMGCoA-RI's	Erythromycin	• Risk of rhabdomyolysis or myopathy	• Reported with lovastatin, but cannot be ruled out with other HMGCoA-RI's.
HMGCoA-RI's	Gemfibrozil	• Risk of myositis, acute renal failure, rhabdomyolysis • BENEFIT MAY NOT OUTWEIGH RISK! • Monitor for symptoms (creatine kinase [CK] normal range 21-235, look for 10x upper limit) • Monitor liver function tests (LFT's)	• Myopathy including rhabdomyolysis reported in up to 5% of lovastatin patients • Interaction also reported with pravastatin
HMGCoA-RI's	Niacin	• Risk of myositis, acute renal failure, rhabdomyolysis • BENEFIT MAY NOT OUTWEIGH RISK! • Monitor for symptoms (CK normal range 21-235, look for 10x upper limit) • Monitor LFT's	• Myopathy reported in 2% of lovastatin patients with or without rhabdomyolysis • Recommend a dose reduction of fluvastatin, simvastatin, and pravastatin
HMGCoA-RI's	Warfarin	• May ↑ effects of warfarin • Risk of ↑ prothrombin time with concomitant use	Reported with both lovastatin and simvastatin

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[f]Li PKT, Mak TWL, Chan TH, et al. Effect of fluvastatin on lipoprotein profiles in treating renal transplant recipients with dyslipoproteinemia. *Transplantation* 1995; 60:652-656.

[g]Davies RA. Safety and efficacy of pravastatin after heart transplantation: Preliminary patients studies.[Abstract] In: *XI International Symposium Drug Affecting Lipid Metabolism*, Florence; 1992:10.

[h]Kobashigawa JA, Brownfield ED, Stevenson LW et al. Effects of pravastatin for hypercholesterolemia in cardiac transplant recipients. *JACC* 1993; 21:141a (abstract).

[i]Yoshimaura N, Oka T, Okanoto M et al. The effects of pravastatin on hyperlipidemia in renal transplant patients. *Transplantation* 1992; 53:94-99.

ATTACHMENT 3

Costs for Hyperlipidemia Drug Therapy (as of November 1996)

For current prices, check the Drug & Pharmaceutical Product
Management Bulletin Board at
708-531-7947

DRUG	USUAL DOSE[a]	FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH
Bile Acid Resins		
Cholestyramine Powder	4 gm bid	$ 18.10
Colestipol Granules	5 gm bid	$ 18.10
Colestipol Tablets	4 gm bid	$ 18.10
HMG CoA Reductase Inhibitors		
Fluvastatin	40 mg qd	$ 21.75
Lovastatin	20 mg qd	$ 26.68
Pravastatin	20 mg qd	$ 26.67
Simvastatin	5 mg qd	$ 21.11
	10 mg qd	$ 26.67
Niacin	1 g IR tid	$ 3.60
	500 mg SR tid	$ 2.75
Gemfibrozil	600 mg bid	$ 5.20

[a]Usual doses; does not reflect equivalent doses.

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Medical Advisory Panel Member

Christine Chandler, PhD
Clinical Specialist/PPM

Bruce Schrader, PhD
Clinical Specialist/PPM

Medical Advisory Panel for the Pharmacy Benefits Management
Strategic Health Group

Mission

The mission of the Medical Advisory Panel (MAP) for Pharmacy Benefits Management (PBS) includes the development of evidence-based pharmacological management guidelines for improving quality and providing best-value patient care.

The MAP is comprised of practicing VA physicians from facilities across the nation:

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VHA PHARMACY BENEFITS MANAGEMENT
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